American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*

Thomas D Giles *Assistant Editor*

International Editorial Board

VOLUME 89

JANUARY-JUNE 1975

VOLUME 89

Printed in the United States of America

January 1975

American Heart Journal

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"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluations 1971 First Edition
Chicago American Medical Association p 121

Kay Ciel® Elixir is potassium chloride... tastes good too!

COMPOSITION Each 15 cc (one table spoonful) contains potassium chloride 1 5 Gm supplying 20 mEq of elemental potassium in a cherry flavored palatable base alcohol 4% Contains no sugar
INDICATIONS Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy digitalis intoxication low dietary intake of potassium or as a result of excessive vomiting and diarrhea
CONTRAINDICATIONS Impaired renal function untreated Addison s Disease dehydration heat cramps and hyper kalemia
PRECAUTIONS Potassium chloride should be administered with caution and adjusted to the requirements of the indi vidual patient since the amount of defi ciency and corresponding daily dose is often not known Excessive or even thera peutic dosages may result in potassium intoxication Patients should be frequently checked and periodic ECG and/or plasma potassium levels made High plasma con centrations of potassium ion may cause cardiac depression arrhythmias or arrest Use with caution in patients with cardiac disease In hypokalemic states attention should be directed toward the correction of the frequently associated hypochloremic alkalosis
SIDE EFFECTS Vomiting nausea abdominal discomfort and diarrhea may occur Symptoms and signs of potassium intoxication include listlessness mental confusion paresthesia of the extremities weakness of the legs flaccid paralysis fall in blood pressure cardiac arrhythmias and heart block When hyperkalemia exists it should be promptly treated with the discontinuance of potassium adminis tration or other steps to lower serum levels if indicated since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias
DOSAGE AND ADMINISTRATION Adults one tablespoonful (15 cc) diluted in one glass of water twice daily after the morning and evening meal Larger doses may be indicated according to the indi vidual patient s requirements but should be administered under close supervision due to the possibility of potassium intoxi cation Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury
HOW SUPPLIED One pint and one gallon bottles



Cooper Laboratories Inc Wayne N J 07470/Ste Therese P Q Canada

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Vol 89 No 1 January 1975 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141

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IN ANGINA* **ACTS WITH SUBLINGUAL SPEED**

CHEWABLE SORBITRATE® 5MG
ISOSORBIDE DINITRATE

As with sublingual ISDN

acts in 2 minutes for therapeutic use
acts up to 2 hours for prophylaxis

In addition

chewing action helps distribute nitrate over a larger mucosal area

SUMMARY OF PRESCRIBING INFORMATION

Mode of action *The* mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks with concomitant reduction in nitroglycerin intake.

* **Indications** Based on a review of this drug by The National Academy of Sciences–National Research Council and/or other information FDA has classified the indications as follows:

Probably effective: Sublingual and chewable dosage forms of SORBITRATE are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less than effective indications requires further investigation.

Contraindications A history of sensitivity to the drug.
Warnings Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.
Precautions Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally Cutaneous vasodilation with flushing, transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension. Individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect). drug rash and [illegible]

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration Route: Sublingual, oral and chewable tablets.

Individual Dose To minimize hypotensive responses which may occasionally be severe with chewable doses as low as 5 mg, the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally 5 to 10 mg is the range commonly used although doses of up to 30 mg have frequently been employed.

Dosage Schedule Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals. Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect Sublingual and Chewable 2 to 5 minutes. Oral 15 to 30 minutes.

Duration of Effect Sublingual and Chewable 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.



STUART PHARMACEUTICALS
Division of ICI United States Inc
Wilmington, Delaware 19897

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March, 1975

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New *Equipment Cart* conveniently houses Ekoline 20A and Recorder. Permits complete system to be readily moved to any location throughout the hospital

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New Multi Parameter [illegible] Module provides the capability for echo, EKG, *phono and carotid pulse* or apex traces

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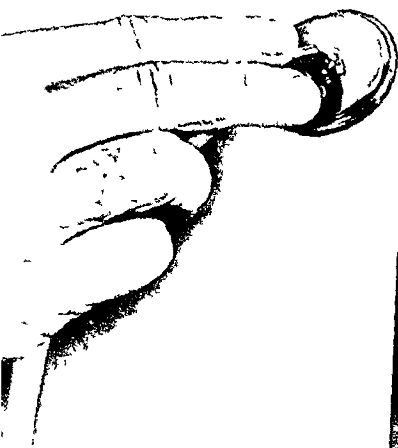
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Accepted Concepts in Angina Therapy*

- Nitrates are the first line of defense against angina pectoris
- The therapeutic goal of oral nitrate therapy is an angina-free patient

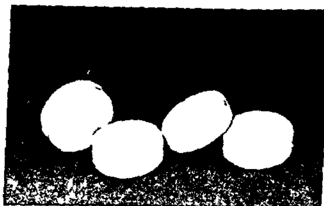
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Because higher dosage often is necessary to achieve this goal IVES LABORATORIES INTRODUCES



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Fewer tablets for patients on 80 mg or more per day (up to a maximum of 120 mg /day)

- To provide prophylaxis against anginal attacks often caused by unavoidable everyday stress
- *To reduce the frequency and severity* of angina pectoris attacks (Not intended to abort the acute episode)

***Indications** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information FDA has classified the indication as follows
Possibly effective When taken by the oral route *Isordil is indicated* for the relief of angina pectoris (pain of *coronary* artery disease) It is not intended to abort the acute anginal *episode* but is widely regarded as useful in the *prophylactic treatment of angina pectoris*
Final classification of the less than effective ind cations requires further investigation

Contraindication Idiosyncrasy to this *drug*
Warnings Data supporting the use of *nitrites during* the early days of the acute phase of myocardial infarction (*the period during* which clinical and laboratory *findings a e unstable) are insufficient to establish* safety
Precautions *Tolerance to thi* drug and cross tolerance to other nitrites and nitrates may occur

Adverse Reactions Cutaneous vasodilation with flushing *Headach* is common and may be severe and persistent Transient episodes *of dizzin ss* and weakness as well as other signs of *cerebral ischemia* associated with postural hypoten ion may occasionally develop *This drug can act as a physiological antagonist to norepinephrine acetylchol ne histamine* and many other agents An occasional individual exhibits marked ensitivity to the hypotensive *effects of nitrite* and severe *responses (nausea* vomiting *weakness* restlessness pallor perspiration and collapse) can occur *even* with the usual therapeutic dose Alcohol may *enhance this effect* Drug *rash and/or exfoliative* dermatitis may *occasionally occur*

Consult direction circular before prescribing

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New York New York 10017

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THROUGH MEDICINE

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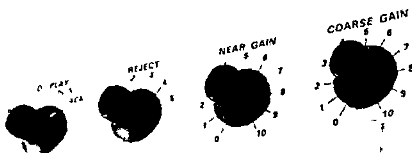
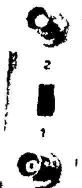
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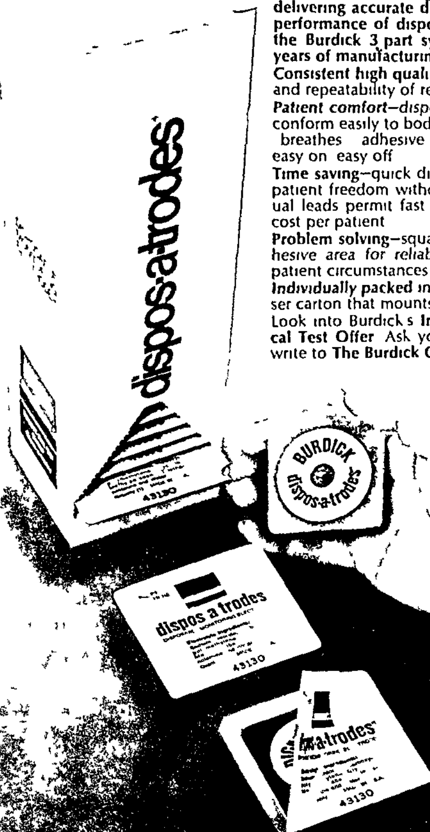
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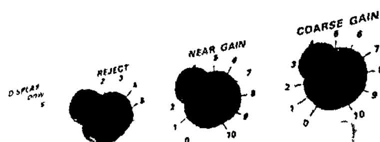
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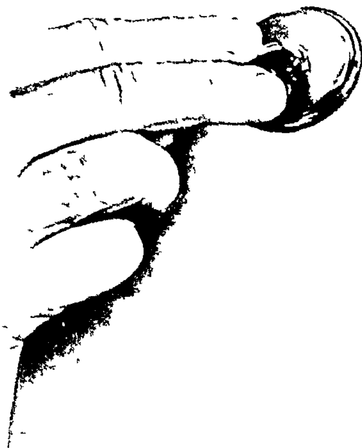
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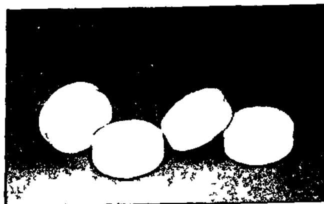
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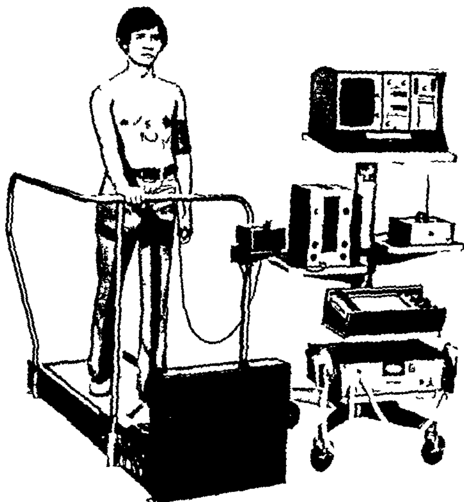
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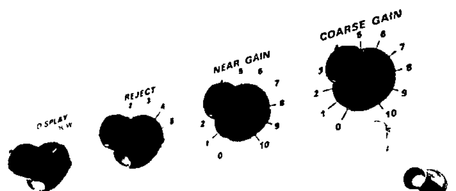
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June 1975

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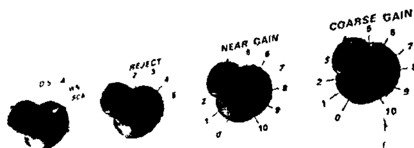
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January 1975 Volume 89 Number 1

Editorial

Use and abuse of diuretics

Edward D Frohlich M D
Oklahoma City Okla.

Over the past two decades pharmaceutical advances have permitted the clinician to be able to promote diuresis by altering nephron function at practically every anatomical level (Table I) However over this time the agents which have been developed are more potent and have been associated with the potential for rather severe clinical complications Hence the prediction and admonition of Dr Robert Berliner (made in 1965 in his American Heart Association lecture Modern Diuretics Use and Abuse)[1] is most worthy of restatement it could not be more meaningful today

'The vast majority of patients in whose treatment the use of diuretics is indicated are well managed with the thiazide group of drugs and have little to gain from the availability of new and more powerful agents Such agents should find their immediate place where currently available therapy is inadequate and should replace currently satisfactory treatment only when it has been shown that the hazards do not exceed the limited potentialities for improvement. The tendency to switch to the newest and most potent agent available could, in this area, lead to a situation in which striking benefits to a few patients are more than outweighed by the unnecessary problems incurred in the many others [1]

Indeed, the warning was most appropriate and correct over the succeeding decade we have witnessed the introduction and wide acceptance of several new and more potent diuretics With their use there has been ample evidence of their hazardous consequences and a parallel disregard of the continued value and indications for the use of the thiazide congeners

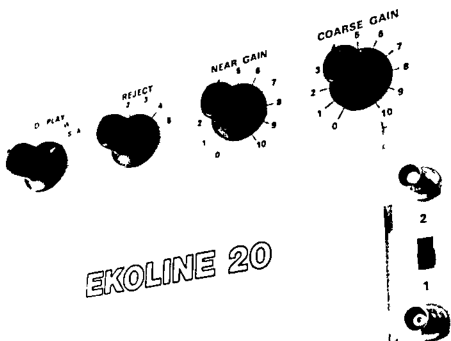
It is out of the scope of this editorial to outline each of the available diuretic agents and their mode of action and it would only detract from its purpose to elaborate upon certain of the more common uses and abuses of all diuretics by clinicians in the academic as well as in the practicing sectors of medicine Suffice it to say these agents have dramatically reduced morbidity and mortality rate from a wide variety of edematous and non edematous cardiac renal endocrine and gastrointestinal diseases—a most apparent statement to all practicing physicians However what perhaps requires specific reemphasis is a listing of some of the more frequent and important problems associated with their use disorders of potassium balance (hyperkalemia and hypokalemia) volume depletion and hyponatremia, hyperuricemia and gout, and hyperglycemia and diabetes mellitus Not detailed are the less fre

From th Hypertension Divi ion D partm nt of Med cine The Univers ty of Okl homa H lth Sciences Cente Okl homa C ty Okla.

Supported, in part, by a grant from the N tio l H art nd Lung In tit te (HL-14311)

Rec ved for publication Jan. 22 1974

Repri t req ests to Edw rd D Frohl ch M D Professor of Medicine The Uni ers ty of Oklahoma, H alth Scie ces Cente P O Box 26901 Oklahoma City Okla. 73190


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Received for public tion J n. 22, 1974

Reprint requests to Edw d D Frohl ch M D Professo of Medici Th Uni rs ty of Oklah m Health Sc en es Center P O Box 26901 Oklahoma City Okla 73190

Table I Effect of different diuretic and natriuretic agents on varying anatomical levels of nephron function

Anatomical level	*Agent*
Renal artery (renal blood flow)	Digitalis xanthines aminophylline
Glomerulus (filtration rate)	Water load osmotic diuretics
Proximal convoluted tubule	Mercurials thiazide congeners
Loop of Henle	Furosemide ethacrynic acid
Distal convoluted tubule	Thiazide congeners spironolactone carbonic anhydrase inhibitors (each with different modes of action)

quent and perhaps more peculiar (or idiosyncratic), adverse effects associated with specific *compounds*

Recently I had the opportunity to visit a very modern community hospital which was fully equipped with computers to facilitate patient care, laboratory reporting, medical record keeping and administration Through this remarkable computer system it was also feasible to identify immediately certain therapeutic problems It was therefore possible for my host to display for me, instantaneously the complete population census of the intensive cardiac care unit each of the respective patient s third party sponsors, his laboratory and clinical records, as well as his therapeutic history One patient, a 54 year old man, had sustained an acute myocardial infarction associated with ventricular arrhythmias earlier in his hospitalization which was also complicated by mild cardiac failure fortunately, he had normal renal function His treatment included mild sedation anticoagulants, digitalis, quinidine, and furosemide To be reemphasized was his normal renal function (blood urea nitrogen 17 mg per 100 ml) however, he demonstrated hypokalemic alkalosis resulting probably from the secondary aldosteronism of the cardiac failure *and* the potent kaliopenic diuretic I was unable to determine the reason for his physician s preference of furosemide to a thiazide diuretic but I did determine that furosemide exceeded the total in hospital diuretic prescriptions (thus far that year) with respect *to all* thiazide congeners by a ratio of 1 783 to 92 It may be argued that furosemide might have been more useful earlier in that patient s hospitalization when he was in mild heart failure, furosemide is valuable in the treatment of acute pulmonary edema because of its rapid action However, this patient was not *in such a severe state of* cardiac decompensation, and once he had become well compensated with that diuretic and digitalis, a switch to a thiazide congener would have been wiser Therefore, I cannot conceive of a better confirmation (anecdotal though it is) of Dr Berliner's forecast than this experience Indeed, subsequent rechecks in other hospitals and community pharmacies have further confirmed this rather common clinical experience

Review articles, specific clinical reports and textbooks concerning diuretic therapy are replete with admonitions that particular caution must be paid to the potential hazards of hypokalemia in cardiac patients who are concomitantly treated with diuretics and digitalis and their predisposition to arrhythmias if the state of potassium balance is not carefully considered and corrected[2] Then why is it that, in the absence of renal failure, the 'loop diureties' are prescribed in preference to the thiazides? And why is it that two or more potassium depleting diuretic agents are *not infrequently prescribed* simultaneously in their full dosage? There can be no reasoned answer to these question *Clearly*, what is needed is a restatement that the vast majority of patients requiring diuretics *can be* 'well managed *with the thiazide group* of drugs and have little to gain from the availability *of* new and more powerful agents "[1] As indicated above, injectable preparations of the 'loop diuretics, furosemide and *ethacrynic* acid may be the *agents of* choice to effect an immediate diuresis in the cardiac patient with acute left ventricular failure and expanded intravascular volume[3] but with *recompensation* diuretic therapy may be continued thereafter with any of the thiazide congeners (alone or with spironolactone or triamterene *to counteract* hypokalemia) And even with the use of the thiazides serum potassium *concentration should be followed carefully in the cardiac patient* receiving digitalis and the so called ' loop diuretics are all the more potent

If this be the lesson from the digitalis compensated cardiac patient then what could be the in*dication for* selecting these agents (the loop diuretics) in the uncomplicated, nonedematous hypertensive patient who faces decades of

diuretic antihypertensive therapy? Yet under these circumstances it is well known that those agents constitute a large percentage of the validly prescribed diuretics (Specifically excluded from this term of validly prescribed diuretics are certain unwarranted uses including the prescription of diuretics for weight reduction and cyclical edema) Indeed, the recent guidelines for the standard treatment of the uncomplicated hypertensive patient subscribed to by the High Blood Pressure Education Program, the American Heart Association the American College of Physicians the American College of Cardiology, and the American Medical Association specifically recommend the *thiazide class of diuretics* without including the loop diuretics [4,5] Particular effort was made to note that "furosemide or ethacrynic acid should be reserved for special circumstances in which a more potent natriuretic effect is required such as in patients with renal failure [5] Yet it has become a general practice of most physicians in academic as well as nonacademic medicine to prescribe these more potent natriuretic agents almost reflexively We must remember that the thiazide congeners continue to remain effective in the vast majority of patients This therapeutic concept is especially important as we anticipate that large segments of the massive hypertensive population (projected as large as 23 million human beings) may be followed by paramedical assistants. Thus why unnecessarily complicate the therapeutic program by selecting potent diuretic agents having potentially greater hazards?

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Clinical communications

The development of cardiac myxomas and papillary endocardial lesions from mural thrombus

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This study originated in an attempt to resolve a controversy among the authors as to the nature of atrial myxomas Polar opinions, similar to those expressed by others were held as to the neoplastic[1 12] versus thrombogenic[13] origin of the lesions In an initial review of material from cardiac tumors of all types it seemed to us that myxomas and papillary endocardial lesions were variations of the same lesion and that both could be explained as organized mural thrombi modified by the mechanical forces to which they were exposed

The intraluminal pressure in the capillary bed of the granulation tissue which grows into an atrial mural thrombus would exceed the pressure of its surroundings and the intracavitary pressure There would be an influx of fluid morphologically appearing as edematous ground substance into the lesion A rapid expansion of the lesion beyond the blood supply derived from the basal granulation tissue would result and a central acellular zone would appear covered by a cortex of mesenchymal cells nourished by intra atrial blood The mesenchymal cells of myxomas would be exposed to mechanical stimuli, and their direction of differentiation might depend on the nature of the stimulus[14 16] Papillary endocardial lesions which appear to develop from non bacterial thrombotic endocarditis have some histologic features similar to myxomas but differ in that vessels do not grow into their bases They more closely resemble the common Lambl's excresence

Autopsy and surgical pathology material from two institutions was reviewed to study the morphologic features of cardiac myxomas and papillary endocardial lesions Particular attention was given to regional differences within the lesions Every such lesion examined appeared consistent with development from an organized mural thrombus

Observations

The available histologic material from indexed cardiac tumors and mural thrombi in the autopsy and surgical pathology files of The Johns Hopkins Hospital and the indexed cardiac tumors of the Vanderbilt University Hospital were reviewed Of the total of 565 specimens examined 466 were classified as mural thrombi 66 as non bacterial thrombotic endocarditis (NBTE) 25 as myxomas and 12 as papillary endocardial lesions Hematoxylin and eosin stains were available in all cases Verhoeff van Gieson elastic (VVG) Masson connective tissue reticulum Alcian blue, periodic acid Schiff phosphotungstic acid hematoxylin and iron stains were prepared for selected specimens

Mural thrombi Mural thrombi of varying ages from all chambers of the heart were studied Most had developed in association with myocardial infarcts or atrioventricular valve stenosis In some instances however no underlying disease was apparent The thrombi seemed to occur most frequently at sites of potential endothelial injury due to surface surface contact as near the fossa

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ovalis (Fig 1) at the line of closure of valve leaflets (Fig 2) or between trabeculae carneae in the ventricles (Fig 3)

The stages observed in the organization of mural thrombi were indentical to those previously noted (Fig 4)[17] The fresh thrombus consisted of a complex aggregate of platelets forming coral like structures leukocytes adherent to the margins of the platelet masses and strands of fibrin looping between the platelet masses and entrapping red cells In later stages a large number of small vascular channels and mesenchymal cells entered the thrombus from its endocardial attachment It was not unusual to see multiple walled vascular channels Foci of hematopoiesis and hemosiderin deposition were common Occasional thick walled vessels were observed at the site of attachment of the organizing thrombus Collagen and elastic fiber formation was prominent in the later stages as the thrombus became converted to a slightly elevated fibrous plaque covered by endothelium

In many instances even in the absence of an associated myocardial infarction damage to the endocardium and myocardium beneath the overlying mural thrombus had occurred. As a result in the final stages of organization of many thrombi granulation tissue and scarring of the cardiac wall merged with the vascular and fibrous tissue of the thrombus and no distinct boundary was apparent

Nonbacterial thrombotic endocarditis and papillary endocardial lesions The lesions most commonly occurred along the lines of closure of the atrioventricular or semilunar valves. The early stages were histologically similar to those of the mural thrombi on the endocardium of the chambers and were generally classified as nonbacterial thrombotic endocarditis (Fig 5 *A*) There appeared to be proportionately more of the coralliform platelet masses and less of the fibrin strands with entrapped red cells in NBTE lesions than in ordinary thrombi NBTE differed greatly from ordinary mural thrombi in that no ingrowth of vascular elements occurred. The papillary nature of the lesion appeared to develop due to contraction or loss of the superficial fibrin layers while the platelet masses persisted and became converted into fibrous filiform papillae (Fig 5 *B*) Each papilla of the mature lesion consisted of a collagenous core covered by an endothelial lining (Fig 5 *C*) Well developed papillary



Fig 1 Thrombus on an incompletely closed foramen ovale at a point of potential endothelium to endothelium contact Viewed from the left atrium

endocardial lesions were histologically indistinguishable from Lambl s excrescences

Myxomas All 25 myxomas occurred in the atria 23 in the left atrium and two in the right atrium Twenty four myxomas were attached to the limbus of the foramen ovale while one arose in the left atrium in direct relation to a point of potential endocardial injury due to a calcific spur on an atherosclerotic mitral valve (Fig 12) Grossly the smaller myxomas had a relatively smooth or slightly lobulated surface The intermediate sized lesions were polypoid or papillary Large myxomas with definite contact with the facing atrial wall again had a relatively smooth surface The size of the myxomas ranged from 1 cm to 8 cm in greatest dimension

In several instances small lesions at the foramen ovale (Fig 1) were unequivocal mural thrombi on histologic examination and were not considered to be myxomas They appeared to have arisen at points of possible contact between endocardial surfaces Other lesions were encountered with microscopic features of both organizing thrombi and myxomas (Fig 6) Small foci of fibrinous material were observed deep in these lesions as well as on the surface The inner part of these intermediate myxomas was composed of an amorphous stroma containing abundant apparently undifferentiated mesenchymal cells and double walled vascular channels The surface showed slight lobulation In intermediate size lesions a definite papillary character (Fig 7) was found. Abundant amorphous interstitial ground substance and fibrin filled the papillary fronds which had central vessels



Fig 2 Nonbacterial thrombotic endocarditis on the line of closure of the mitral valve Note the papillary configuration

Fig 3 Mural thrombus between a trabecula carnea and the ventricular wall of the left ventricle

Large myxomas had distinct zones (Fig 8) The base had a rich vascular network and scattered and clustered macrophages and undifferentiated mesenchymal cells (Fig 9) Beyond the vascular bed an acellular zone with fibrin and interstitial tissue was found The cortex (Fig 10) consisted of cells resembling cartilage embedded in pools of Alcian blue positive material Blood vessels were not present in this layer

The three features which had previously suggested a neoplastic nature of myxomas were also observed in these cases peculiar double wall vessels[1 3 7] invasion of the underlying atrial wall[3 4 7 18] and metastases[' 7 12 19 24] All 25 myxomas showed small vascular channels lined by multiple walls frequently in a concentric arrangement with blood elements identifiable within only the inner space (Fig 11 *A*) Similar structures were found in organizing thrombi and granulation tissue (Fig 11, *B*)

In one case apparent invasion of the left atrial wall was observed (Fig 13) However on serial section, it was found that the myxoma was confined to the lumen of a vein which communicated with the atrium beneath the myxoma No actual penetration of the atrial myocardium could be identified

In four cases embolization by myxoma fragments had occurred In one of these an embolus from a myxoma to the splenic artery had resulted in disruption of the arterial smooth muscle and elastica and appeared to extend into the perivascular soft tissue (Fig 14) However, although this metastatic growth is suggestive of malignant behavior destruction of a muscular arterial wall with growth of organizing thrombus material into the adventitia may also occur as a result of embolization of the thrombus (Fig 15) or foreign material (Fig 16) This was shown by histologic examination of 236 systemic and 135 pulmonary arteries found to contain emboli from 212 different patients in our autopsy files[25] Smooth muscle and elastic damage were observed underlying the emboli in 49 instances False aneurysm formation as a result of penetration of the organizing emboli through the arterial wall into the peri arterial tissues occurred in seven cases There was no evidence of vasculitis or septic emboli in any of these cases A source for the emboli was described in the left atrium left ventricle or aorta and/or multiple emboli were documented in all cases

Discussion

The observations presented in this study provide morphologic evidence of the development of

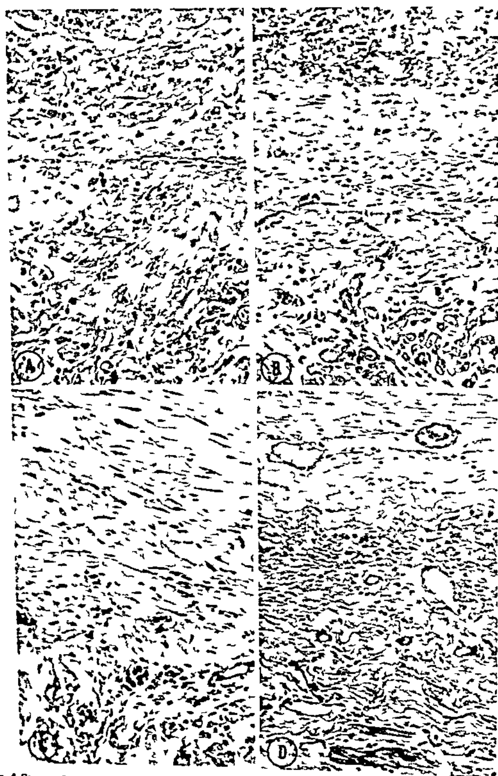


Fig 4 Stages of organization of mural thrombus. *A*, fresh thrombus (top) overlying damaged endo- and myocar
dium with muscle necrosis, elastica fragmentation, and slight inflammation *B* granulation and young fibrous
tissue has replaced myocardium and merges imperceptibly with similar tissue of overlying thrombus *C*, some
granulation tissue persists (bottom) but much of the thrombus and underlying damaged cardiac tissue consists
of loose fibrous tissue and the original limits of endocardium and thrombus cannot be discerned. *D* well devel
oped fibrous tissue comprises thrombus and area of endomyocardial injury with no definite boundary between
the two. (All hematoxylin and eosin, ×?00)



Fig 5 Stages in the development of papillary endocardial lesions *A* portion of nonbacterial thrombotic endocarditis at valvular line of closure (hematoxylin and eosin ×80) *B* papillary endocardial lesion with papillae composed of endothelial covered thrombus material in layers with developing fibrous tissue (hematoxylin and eosin ×40) *C* papillary endocardial lesion or large Lambl s excrescence with numerous thin endothelial covered fibrous papillae Note absence of basilar granulation tissue (Hematoxylin and eosin ×80)

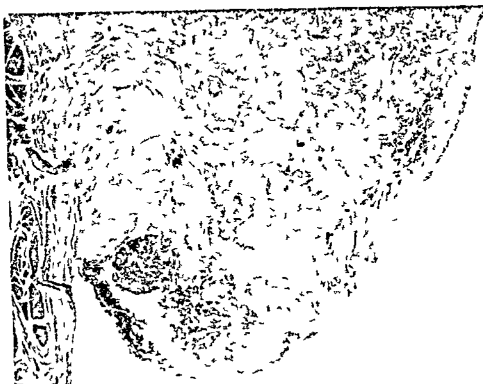


Fig 6 Small left atrial lesion with features of both myxoma and ordinary mural thrombus Smooth superficial border composed largely of granulation tissue and ground substance but with areas of unorganized thrombus material remaining relatively deep in the lesion (hematoxylin and eosin, ×20)

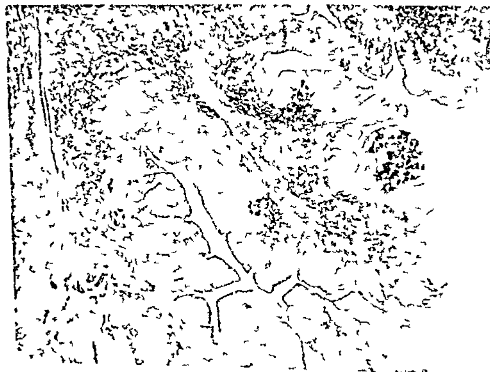


Fig 7 Intermediate sized left atrial myxoma with papillary configuration Granulation tissue in stalk of each papilla and a thin layer of cells superficially with an intervening zone of amorphous ground substance (hematoxylin and eosin, ×15)



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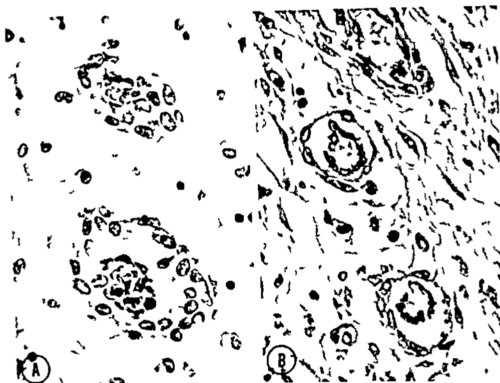


Fig 11 Double walled capillaries set in abundant ground substance and mesenchymal cells in a myxoma (A) and an ordinary left ventricular mural thrombus (B) (Both hematoxylin and eosin ×500)

papillary endocardial lesions and myxomas from thrombi Thrombus material is deposited as a result of endocardial injury regardless of the location Three different sequences of change in endocardial thrombi appear possible (Fig 17) (1) Granulation tissue and mesenchymal cells grow into ordinary mural thrombi from the site of attachment Although slight enlargement may occur as a result of successive layers of thrombus material on the surface the thrombus eventually is converted to a flat fibrous scar due to fibroblast proliferation and collagen deposition (2) The papillary endocardial lesion increases in size as a result of deposition of successive layers of thrombus material. The papillary configuration is acquired gradually as additional thrombus material is added on in some foci and lost in others. No ingrowth of granulation tissue occurs, and the thrombus material of the papillae is finally converted to fibrous tissue (3) As in the ordinary mural thrombus granulation tissue enters the base of thrombi which will develop into myxomas. Like the papillary endocardial lesions the myxomas gradually increase in size and acquire a papillary configuration. However their growth continues because of influx into the lesion of fluid from the basal granulation tissue This results in a central zone of amorphous material in the lesion with a region of granulation tissue on the basal side and a superficial cortical area containing mesenchymal cells nourished by the luminal blood on the other The myxoma acquires a relatively smooth surface when its large size results in contact with the atrial wall

The major difference between ordinary mural thrombi and papillary endocardial lesions was the lack of ingrowth of vascular channels in the latter Its usual location on the relatively avascular valve leaflets may be the explanation of this phenomenon The papillary lesion enlarges and matures by successive platelet and fibrin deposition and conversion to fibrous tissue Both lesions develop an endothelial covering Presumably because of its vulnerable location at the valvular lines of closure the lesion undergoes repeated endothelial injury and enlarges as a result of successive layers of fibrin deposits The ordinary mural thrombus in most instances decreases in size as fibrous tissue replaces the thrombotic material Many of the morphologic features of mural thrombi in the process of organization and myxomas were identical. Both contained amor



Fig 8 The three zones of the large myxoma Inner zone (left) with numerous capillaries, mesenchymal cells, and ground substance Middle acellular layer composed entirely of amorphous ground substance Cortical zone (right) with several layers of mesenchymal cells. (Hematoxylin and eosin ×20)



Fig 9 Inner zone of a large myxoma with thick walled vessels in the wall of the left atrium (left) and the myxoma Also note numerous capillaries mesenchymal cells, and ground substance (Hematoxylin and eosin ×35)

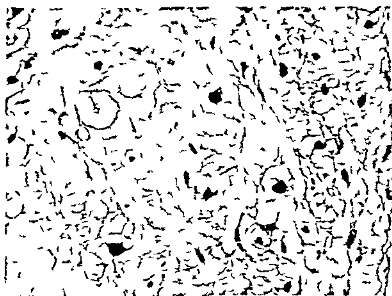


Fig 10 Cortical zone of a large myxoma The mesenchymal cells just below the surface have features suggesting cartilaginous differentiation (Hematoxylin and eosin ×200)

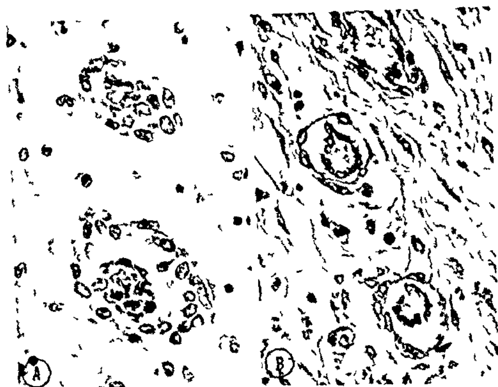


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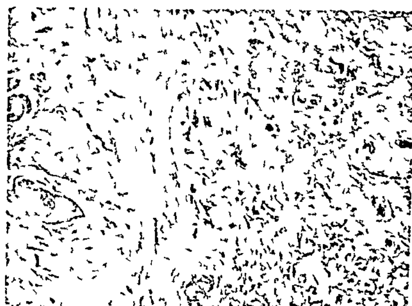


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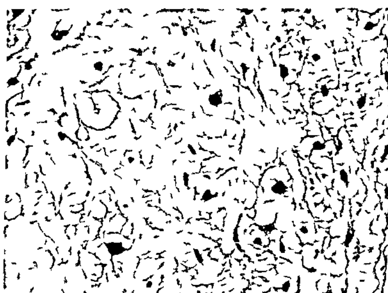


Fig 10 Cortical zone of a large myxoma The mesenchymal cells just below the surface have features suggesting cartilaginous differentiation (Hematoxylin and eosin ×200)



Fig 14 False aneurysm of splenic artery associated with myxoma embolus Smooth muscle and elastic laminae are obliterated by myxoma tissue which extends into peri arterial soft tissue (hematoxylin and eosin ×40)

origin of myxomas from multipotential me senchymal or vasoformative remnants However similar electron microscopic observations have been made in granulation tissue and thrombi[27-33] and it seems likely that multipotential me senchymal cells also enter a fresh mural throm bus The line of differentiation of these me senchymal cells may then depend on local fac tors For example the formation of elastic fibers collagen fibers cartilage or bone appears to be the consequence of the type of mechanical stim ulus applied to the cell[14,17,34-36] In large myxomas with a compression stimulus resulting from encroachment of the lesion on the opposite atrial wall cortical cells with features suggesting car tilagenous differentiation would occur as noted occasionally in our material In rare instances, even bone and bone marrow could develop as described previously[1,4,23] In general the finding of several types of mesenchymal cells in various stages of differentiation is more in keeping with a non neoplastic tissue

Although much of the amorphous matrix of myxomas probably derives from transudation as described earlier the acid mucopolysaccharide-rich component probably is produced by the me senchymal cells of the lesion This is consistent with the electron microscopic demonstration of evidence of secretion in the cells of the lesion[1,11] and with the acid mucopolysaccharide content of mesenchymal ground substance in other loca tions e g normal cartilage[1] and granulation tissue[37] Fine Morales and Horn[3] described the histochemistry of myxoma and stated that the findings differed from those of ordinary thrombi although they did not specify the differences nor discuss the reactions in thrombi Our observa tions of common histochemical stains in thrombi (PAS PAS digest Alcian blue and mucicarmine) did not suggest any differences[37] particularly in myxoid areas of otherwise ordinary mural thrombi[26] Others have noted abundant acid mu copolysaccharide in both granulation tissue[38] and thrombi[39,40]

The major points of evidence usually cited in favor of a neoplastic origin of cardiac myxomas are its usual location at the foramen ovale in the left or right atrium[7,12] the cellular architecture of the lesion with myxoma cells in multiple layers about small capillaries[1-3,7] the apparent invasion of the atrial wall in occasional ins tances[3,4,7,18] and the destruction of peripheral



Fig 12 Cut surface of a left atrial myxoma which has arisen away from the foramen ovale at a potential site of injury to the atrial endocardium from a calcific spur (arrow) projecting above an atherosclerotic mitral valve
Fig 13 Invasion of left atrial wall by myxoma but actually confined to the lumen of a Thebesian vein Mitral valve at lower right corner (Verhoeff Van Gieson ×7) Inset shows wall of vessel with myxoma tissue in the lumen (Verhoeff Van Gieson ×200)

phous ground substance, mesenchymal cells and abundant small vascular channels Similar foci often with a myxoma like appearance occur in organizing arterial and venous thrombi [26] The appearance of these components did not allow separation of mural thrombi and myxomas However unlike ordinary cardiac and peripheral thrombi large myxomas were composed of three distinct zones an inner cellular and vascular layer, a middle acellular layer and an outer cellular layer This layered structure may explain the other feature of myxomas usually absent in ordinary mural thrombi the progressive increase in size The hydrostatic pressure in the vascular bed of an atrial myxoma would be greater than the extravascular pressure resulting in an influx of fluid into the myxoma This could partially explain the abundant amorphous extracellular material observed in myxomas The central acellular layer would result from continued deposition of edematous ground substance beyond the blood supply of the basal granulation tissue The cortical cellular layer could derive its nourishment from the chamber lumen The failure of most mural thrombi, especially atrial thrombi, to develop and enlarge following the same sequence of events is probably due to anatomic position and the rate of granulation tissue ingrowth and collagenization being rapid enough to preclude formation of an expanding acellular zone The relatively avascular nature of the tissues in the vicinity of the limbus of the fossa ovalis may reduce ingrowth into thrombi at that site No blood vessels enter thrombi deposited on the avascular portions of the valve leaflets

The nonvascular cellular components of organizing thrombi and myxomas referred to previously as mesenchymal cells are largely undifferentiated by light microscopy Electron microscopy has revealed that undifferentiated cells cells with features of fibroblasts smooth muscle cells and endothelial cells collagen and elastin of various degrees of maturity are present in myxomas [1 4 5 6 11] These observations have been presented as supporting evidence for a neoplastic

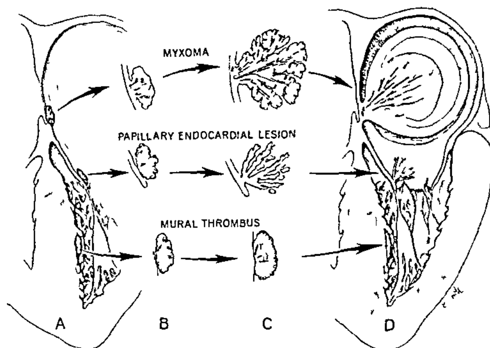


Fig 17 Stages in development of ordinary mural thrombus (bottom) papillary endocardial lesion (middle) and myxoma (top) *A* formation of thrombi at sites of potential endocardial injury—beneath trabecula carnea at valvular line of closure and at foramen ovale *B* slight enlargement of lesions due to successive layers of superficial thrombus deposition ingrowth of granulation tissue at base of ordinary mural thrombus and myxoma *C* granulation and fibrous tissue increase in amount in mural thrombus The papillary endocardial lesion enlarges and its papillary nature develops by continued deposition of thrombus material in some foci and loss of substance in others The myxoma enlarges as does the papillary endocardial lesion in part In addition large amounts of ground substance enter the lesion from its basilar vascular supply which has expanded to send branches into each of the large papillae *D* the mural thrombus is converted to a nearly flat, fibrous scar by fibroblast proliferation and collagen and elastic fiber deposition The stalks of the papillary endocardial lesion are large and composed of dense fibrous tissue and collagen covered by endothelium The myxoma has progressively enlarged mainly by an increase in the ground substance from within Three zones have developed the inner layer is composed of capillaries mesenchymal cells, and ground substance The middle zone is acellular and contains only amorphous ground substance The outer zone is composed of layers of mesenchymal cells with cartilaginous differentiation The surface of the large lesion is relatively smooth due to contact with the atrial walls.

oma may remain in the atrial veins and subsequently enlarge as did the initial lesion In addition apparent atrial invasion could result from the merging of organized thrombus tissue and granulation tissue in the atrial wall Muscle and elastica damage frequently occurs in association with mural thrombi In the healing stage the boundary between the thrombus and the previous limits of the endocardium is indistinct and frequently impossible to identify

Destruction of muscular arterial walls by myxoma emboli has been described and presented as evidence of a neoplastic nature of myxomas [7,12,19,24] However this phenomenon may occur as ordinary thromboemboli undergo organization and is not evidence of neoplasia [25] The explanation of this phenomenon is unknown but may be due either to interference with nutrition of the arterial wall or to substances released from the thrombus itself

Although a thrombogenic theory of origin for myxomas was presented 58 years ago by Thorel [13] virtually all recent authors have concluded or assumed that myxomas are true neoplasms Most authors agree that papillary endocardial lesions are peculiar organized thrombi [12,45] This study presents morphologic evidence which suggests that both papillary endocardial lesions and myxomas do indeed, develop from mural thrombi The morphologic features interpreted as showing the neoplastic nature of myxomas are inconclusive since identical features are found in



Fig 15 False aneurysm of splenic artery as in Fig 14 but the embolus is from an ordinary left ventricular mural thrombus (Verhoeff Van Gieson ×40)
Fig 16 Smooth muscle and elastica damage associated with a foreign body embolus (arrow) in a pulmonary artery (Verhoeff Van Gieson ×270)

muscular arterial walls by myxoma emboli in some cases [7,12,19,24]

The location of myxomas may be explained by the frequent occurrence of redundant cords of endocardial tissue adjacent to the foramen ovale [41] Localized endocardial injury with thrombus formation could result from surface to surface contact at this site It has been shown that endothelium to endothelium contact results in formation of myxoma like growths in dogs [34] In rare instances myxomas arise away from the foramen ovale and may be initiated by other types of endocardial injury such as the mitral valve calcific spur in one of our cases An almost identical relationship is suggested by Figure 33 2 A of Hudson [42] Atrial thrombi would be more likely to develop into myxomas than ventricular thrombi due to the much lower intracavitary pressure in the atria The low atrial pressure would favor accumulation of transudated material within and enlargement of the lesion The uncommon progression of atrial thrombi to myxomas and the occasional occurrence of ventricular myxomas[1,3] suggests that the degree of vascularity of the tissue underlying the thrombus and the rate of granulation tissue ingrowth are important factors determining the final form of a mural thrombus

The cellular arrangements held to characterize myxomas[1,3,7] are found also in ordinary organizing thrombi including thrombi in arteries and veins [26] The peculiar pallisading of cells around a central vascular lumen can not in itself be considered an indication of neoplasia It seems likely that this represents a feature of developing small vascular channels The nonvascular cells of myxomas are mesenchymal cells of various types and provide no conclusive evidence of neoplasia

Apparent invasion of the atrial wall at the myxoma base has been described previously[3,4,7,18] and was observed in one of our cases Serial sections revealed however, that the myxoma was confined to the lumen of a vein which entered the left atrium and was continuous with the main myxoma mass It is probable that this explains at least some of the previously reported cases of atrial wall invasion since mural thrombus material frequently extends into Thebesian veins draining into the chamber beneath the thrombus This may also explain the occasional recurrence[10,43,44] of myxomas after excision since myx

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mural thrombi and their systemic emboli Despite their non neoplastic nature we favor retention of the term cardiac myxoma for these lesions because of their distinctive mode of development from mural thrombus

Summary

A morphologic study of 466 cardiac mural thrombi, 66 examples of nonbacterial thrombotic endocarditis 25 myxomas, and 12 papillary endocardial lesions was performed. It appeared that three different sequences of organization of endocardial thrombi are possible (1) Ordinary mural thrombi are converted into a flat, fibrous scar by fibroblast proliferation and collagen and elastic fiber deposition (2) Papillary endocardial lesions develop from nonbacterial thrombotic endocarditis as additional thrombus material is acquired in some foci and lost in others No ingrowth of granulation tissue occurs at the base of these lesions The thrombus material of the papillae is gradually replaced by fibrous tissue and the lesion eventually is identical to a large Lambl s excrescence (3) Myxomas enlarge in part as do the papillary endocardial lesions In addition their size increases as a result of influx into the myxoma of fluid from the basal granulation tissue Although myxomas cannot be differentiated from ordinary mural thrombi on the basis of the cellular and ground substance components, their mode of development results in a distinctive appearance The mature lesion is composed of three zones a basal layer of small vascular channels undifferentiated mesenchymal cells, and ground substance a middle acellular zone of ground substance and a cortical layer of mesenchymal cells The peculiar arrangement of endothelial cells and undifferentiated mesenchymal cells, the examples of apparent atrial wall invasion and the cases of embolic metastases provide no conclusive evidence of neoplasia, since these features may also be seen with ordinary mural thrombi

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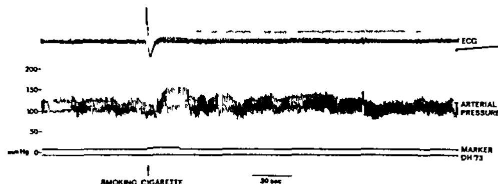


Fig 1 A record from Case 2 The patient having lit his cigarette and inhaled signaled the event Note the fall in arterial pressure and cardiac slowing over 10 beats at that point followed by a tachycardia and upsurge in arterial pressure and finally the heart rate slows again in association with the pressure rise

Table I

Case	*Sex*	*Age*	*Diagnosis*	*Resting BP*	*ECG*	*No of cigarettes*	*Medication*
1	M	54	Angina pectoris	120/80	Ischemia	2 (5)	Glyceryl trinitrate Practolol, 300 mg daily
2	M	45	Labile hypertension	140/100	Normal	15 (20)	Diazepam 2 mg three times a day
3	M	38	Essential hypertension	210/135	Normal	3 (5)	—
4	M	56	Normal	160/80	Normal	2 (10)	—
5	M	61	Chest pain and hypertension	160/100	Normal	2 (5)	Glyceryl trinitrate
6	M	35	Normal	136/84	Normal	1 (3)	—
7	F	26	Labile hypertension	170/115	Normal	4 (5)	—
8	M	41	Coarctation of aorta	230/120	LV+	8 (10)	—
9	M	35	Normal	140/90	—	12 (15)	—

Clinical details of the nine patients The number of cigarettes listed is that for which observations were made in this study the average daily consumption is given in brackets

beats at the minute before smoking and at the fifth minute after smoking The immediate pattern is the response elicited within a few seconds of the first inhalation of tobacco smoke in which the extreme values of blood pressure are calculated the heart rate is considered as a mean of five to ten beats during these variations of arterial pressure To compare the two sets of readings the t test for paired samples was used.

Results

Long term events

Heart rate There was no certain pattern of change in heart rate the heart rate slowed in 23 instances increased in 20 instances and remained the same in the remaining six instances Thus, our data as a whole show no significant difference after smoking a cigarette (+0 8 beats per minute t = 0 59) (Table II) However certain short term changes were observed and will be discussed

Arterial pressure Tobacco smoke under the various conditions of everyday life almost always caused an increase in both systolic and diastolic pressure with only a few exceptions We did not find a difference in behavior between normotensive and hypertensive patients (Table II)

SYSTOLIC Our data show that there was a mean increase of 10 7 mm Hg five minutes after starting smoking as compared with the pressure immediately preceding smoking (t = 6 0 P < 0 001)

DIASTOLIC There was a mean increase of 5 3 mm Hg in diastolic pressure five minutes after starting smoking (t = 5 0 P < 0 001)

Short term events A particular pattern in the behavior of arterial pressure and heart rate was seen during the smoking of 17 cigarettes by four

Direct arterial pressure, heart rate, and electrocardiogram during cigarette smoking in unrestricted patients

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Over the last 30 years there has been in both animals and man, a continuing interest in the cardiovascular effects of cigarette smoking The subject is well reviewed[1,2] It is generally agreed that nicotine causes a significant increase in heart rate and a rise in both systolic and diastolic blood pressure which is thought to result from stimulation of sympathetic ganglia But all these studies were made in the laboratory under carefully controlled conditions with the inherent subjective effects on arterial pressure and heart rate In this paper, we describe the behavior of arterial pressure heart rate and the electrocardiogram (ECG) during cigarette smoking in nine subjects who were free to do as they pleased in their activities

Patients and methods

Nine patients who were regular smokers and who always inhaled freely consented to this study after it had been fully explained to them their involvement being a 24 hour continuous recording of arterial pressure heart rate, and ECG Clinical details of these patients are presented in Table I

The methods used for measuring direct arterial pressure and the electrocardiogram in unrestricted patients have been fully described in previous publications[3] Briefly, a Teflon catheter (length 10 cm, internal diameter 0 9 mm) was inserted into the left brachial artery using the Seldinger technique The catheter was connected to a transducer and perfusion pump by a 1 M length of Teflon tubing 0 35 mm internal diameter and was perfused with normal saline at about 1 5 ml per hour The recording system was a miniature (four channel analogue) tape recorder using standard compact cassettes. The transducer perfusion pump, and tape recorder were carried in a padded harness at heart level the reference point for pressure was therefore constant irrespective of the position of the arm The frequency response of the whole system was flat to 10 Hz The ECG system consisted of bipolar electrodes placed over the V5R V5L positions Leads were held in place by electrode discs and secured by surgical tape to minimize movement artifacts The tape cassettes were replayed on a separate playback deck at 25 times the recording speed The output from this playback deck was fed into an ultraviolet recorder so that compressed or expanded records for beat to beat analysis might be obtained The patients were all studied over a 24 hour period from 9 A M to 9 A M During this time they attended the laboratory only once for 15 minutes after a 12 hour period in order to apply a calibration to the tape and to service the perfusion chamber

Cigarette smoking episodes were selected for analysis only if they were clearly signaled by the patient Each episode was inspected on a beat to beat basis, for one minute before smoking during smoking and five minutes after smoking The long term response is calculated as a mean of 20

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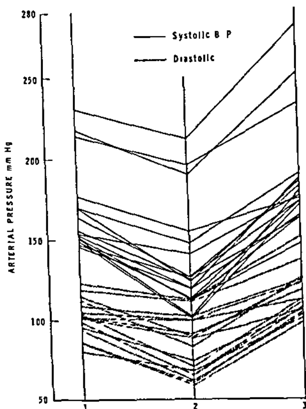


Fig 2 A summary of the changes in arterial pressure which occurred immediately following the first inhalation of tobacco smoke in 17 instances this emphasizes the fall and subsequent rise in pressure to beyond the control levels The pressures were measured at the extremes 1 = control 2 = lowest pressure and 3 = highest pressure

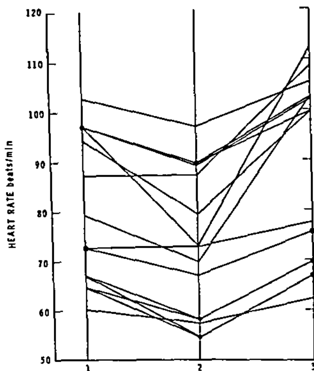


Fig 3 A summary of the heart rate changes corresponding with the arterial pressure levels of Fig 2 The final cardiac slowing which occurs in this sequence is not indicated here O = two separate readings

20 beats per minute) in contrast with the substantial increases reported by others (mean increase 36 beats per minute)[4] However we have to remember that our subjects were unrestricted in their movements while those investigated in the laboratory were relaxed lying at rest and usually smoked two cigarettes in quick succession One of our patients (Case 8) smoked two cigarettes one following the other and the heart rate increased from 80 to 88 beats per minute while the blood pressure increased from 172/123 to 205/128 mm Hg Frankl Friedman and Soloff[7] did not find any significant alteration in blood pressure or heart rate after smoking cigarettes in the nonbasal state as opposed to observations in the resting basal state in the same laboratory[8] The authors attributed this finding to the fact that their nonbasal subjects were already stimulated by the anxiety created by such studies in a laboratory environment which produced significant rises in cardiac output and arterial pressure before the cigarettes were smoked We have found an almost constant increase in arterial pressure during cigarette smoking despite the fact that our patients were completely uninhibited and in no way could they be considered to be in a basal state (Table II) We found that a notable exception to the almost constant increase in arterial pressure was present during the period spent in bed before sleep by Case 8 in which while the first cigarette is still able to increase the arterial pressure the second is not able to reverse the pattern of a continuously descending pressure which characterizes the period before sleep (Fig 7) The pattern of behavior of arterial pressure and heart rate observed during the first few moments of smoking is of particular interest (Figs 1 and 2) A rise in blood pressure was clearly preceded by a small fall following the first inhalation of the cigarette smoke This pattern was observed in varying degree in four individuals during 16 smoking incidents (Cases 2 7 8 and 9) In cats anesthetized with chloralose the rise in blood pressure caused by intravenous nicotine is frequently preceded by a small fall which has been attributed to stimula

Table II

Case	Arterial pressure (mm. Hg)		Heart rate (min.)	
	Before	After	Before	After
1	150/90	178/97	65	70
	172/120	170/127	71	88
2	156/103	158/103	71	69
	156/101	156/101	55	61
	146/98	174/108	71	60
	160/125	182/121	62	65
	158/95	150/105	63	63
	140/100	180/110	77	71
	147/80	157/87	63	52
	175/105	162/110	63	63
	147/102	176/116	76	72
	155/102	185/104	77	58
	152/85	159/89	69	64
	149/86	152/90	56	61
	146/89	173/105	61	68
	153/86	167/92	63	61
	128/72	149/86	76	61
3	232/189	232/185	80	93
	205/131	226/141	77	71
	181/116	212/138	77	77
4	141/86	147/87	69	71
	124/85	134/90	68	63
5	107/54	109/55	71	69
	90/61	112/65	91	88
6	132/80	143/84	65	63
7	146/103	150/106	90	98
	133/88	138/93	92	80
	147/101	173/113	80	95
	150/102	140/97	78	74
8	205/88	200/98	80	75
	218/102	235/104	84	93
	205/91	225/114	84	86
	217/111	233/114	80	91
	221/117	238/124	91	86
	234/127	232/126	91	84
	172/123	177/126	91	84
	177/126	205/128	84	88
9	138/93	153/103	93	107
	121/77	124/81	78	98
	128/93	138/100	110	110
	130/95	145/93	101	118
	107/77	104/67	110	98
	96/61	106/71	114	114
	101/69	123/72	110	118
	119/79	123/77	104	104
	147/92	158/101	104	117
	156/103	136/92	104	89
	135/81	155/93	78	86
	139/88	151/95	80	98

A summary of the changes in arterial pressure and heart rate five minutes after smoking a cigarette

individuals (Cases 2, 7, 8 and 9) This consisted of a brief fall in arterial pressure occurring over 8 to 10 heart beats (mean for group 31/19 mm Hg) following immediately after the first inhalation of tobacco smoke, followed by a rebound rise in systolic and diastolic pressure to a level greater than the presmoking level (mean 51/33 mm Hg) (Figs 1 and 2) There was a bradycardia accompanying the initial fall in pressure (mean eight beats per minute) followed by a tachycardia as the pressure reached its nadir and began to rise again (mean 15 beats per minute) and finally there was usually a second bradycardia accompanying the rise in arterial pressure beyond the presmoking levels (mean nine beats per minute) (Fig 3)

Arrhythmias No significant arrhythmias were observed during any of the smoking episodes

Electrocardiographic changes One patient (Case 1) developed angina pectoris after cigarette smoking and showed ST segment depression preceding the subjective appreciation of pain (Figs 4 and 5) No significant change was found in any of the other patients

Discussion

As a result of laboratory studies in animals and man, smoking is generally believed to produce a rise in arterial pressure and an increase in heart rate [1] The patients taking part in our study were completely free to do as they pleased throughout the 24 hours, and since they were unaware that their smoking was being specifically investigated we believe that smoking only was responsible for any changes observed

Our new system of continuously recorded arterial pressure and heart rate enabled us to observe not only the long term alterations induced by tobacco smoke but also other short term events which are obviously missed with the classical use of a sphygmomanometer for the determination of the arterial pressure and also with arterial catheterization if a continuous monitoring is not performed

The increase in both systolic and diastolic pressure that we have observed was generally less than that recorded by the majority of other investigators [1 4 5] but is in keeping with the findings[6] which reported mean increases of systolic and diastolic pressure of 5 2 and 3 2 mm Hg respectively after smoking In our observations heart rate changes are variable (range ± 10 to

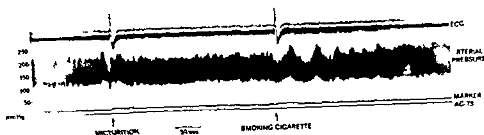


Fig 6 A tracing from Case 8 showing both micturition and cigarette smoking Note the initial fall and subsequent rise in pressure associated with the early phase of smoking This pattern was repeated several times in this instance each possibly associated with inhalation Compare these changes with those occurring with micturition which we have found to consist predominantly of a Valsalva maneuver

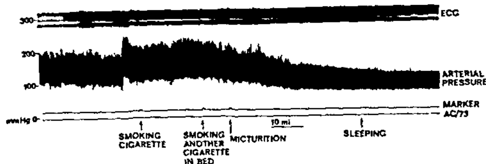


Fig 7 A tracing from Case 8 showing that the rise in pressure associated with the first cigarette is not repeated when the patient is lying in bed Micturition was performed into a chamber pot at the side of the bed and is associated with a brief rise in pressure Note the profound fall with sleep

the reflex response being vagal in origin Two different pathways were involved viz the vagus and the sympathetic nerves of the blood vessels Nasal inhalation of a large bolus of nicotine caused the heart rate to fall and the mean arterial pressure to rise in the unanesthetized rabbit and dog and in man [13] There were differences in quantitative effects man responding the least In the rabbit the typical response to inhaled nicotine was reflex apnea in expiration bradycardia and a rise in mean arterial pressure with a widespread reduction in blood flow and peripheral conductance It has been demonstrated that the apnea was due to direct suppression of respiratory neurones by trigeminal activity mainly in bulbospinal regions with the cardiovascular changes being due to direct trigeminal arterial basoreceptor interactions and to lung inflation arterial basoreceptor interactions in both suprabulbar and bulbospinal regions [13] These results in man also suggested that in certain circumstances nasopharyngeal stimuli can evoke strong cardiovascular reflexes

This work offers an explanation for the rise in arterial pressure observed during smoking but fails to account for the transient fall that we have observed in some of our smoking episodes and also those clearly documented by Armitage and Hall [2]

An alternative explanation could be that the observed pattern was produced by the process of deep inhalation or exhalation such as would occur with a Mueller or Valsalva maneuver However we were able to perform these maneuvers at the end of the 24 hour study in two of our patients who showed the particular pattern during smoking and the results were quite different (Fig 8) We believe that our observations demonstrate the presence of a cardiorespiratory reflex following the inhalation of tobacco smoke in some instances This pattern occurred in two patients with labile hypertension one with coarctation of the aorta and one who was normotensive Our numbers are too small to make any firm conclusions from this

The generalized rise in systolic and diastolic pressure was seen in both normotensive and hypertensive patients unlike Hines and Roth [14] we did not find any significant quantitative differences between the two groups Hines and Roth[14]

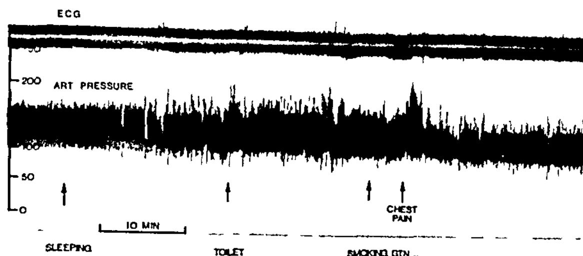


Fig 4 Angina pectoris followed cigarette smoking in Case 1 Note the acute pressure rise associated with the *subjective* appreciation of pain suggesting an acute vasoactive phenomenon

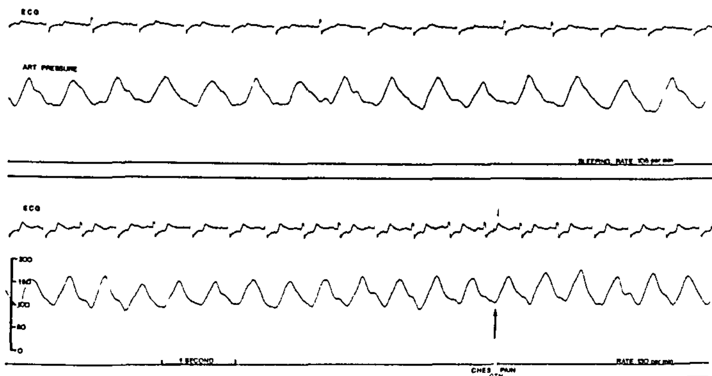


Fig 5 A beat to beat analysis from Fig 4 indicating that significant ST segment depression had occurred in the ECG before the *subjective* appreciation of pain

tion of vagal ganglia[9] and is accompanied by bradycardia and transient apnea Nicotine also causes a fall in blood pressure when injected into coronary circulation [10] right atrium [11] or intravenously into the encéphale insolé preparation in the cat [12] Recently it has been found[2] that nicotine (5 to 20 μg per kilogram) injected into the femoral vein or pulmonary artery of cats anesthetized with chloralose usually caused a fall in blood pressure within a few seconds the fall being followed by a much larger rise When similar amounts of nicotine were injected into the left atrium there was usually no initial fall in blood pressure, neither was there an initial fall with its introduction into the lungs by tobacco smoke But in five out of 15 experiments the initial rise in arterial pressure induced by tobacco smoke and intravenous nicotine was preceded by a slight fall before the rise but for the same rise in arterial pressure the initial rise was greater for intravenous nicotine than for tobacco smoke Analysis of this nicotine depressor response[2] showed that it was due to stimulation of sensory nerve endings in the lungs the afferent nerve of

following immediately after the first inhalation of tobacco smoke followed by a rebound rise in arterial pressure to a level greater than the presmoking level this is probably a vagal effect Cigarette smoking caused angina pectoris in one individual and the records showed ST segment depression in the ECG before the subjective appreciation of pain

We are grateful to Mr Robin Carter for technical assistance

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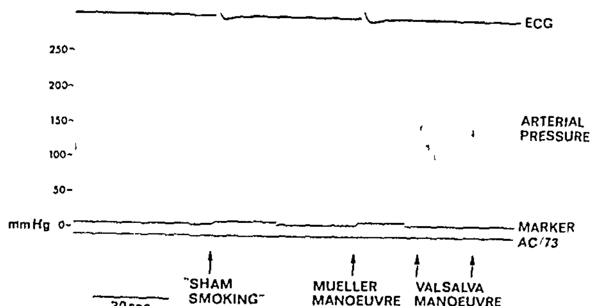


Fig 8 A beat to beat analysis of a series of deliberate maneuvers at the end of a 24 hour study in Case 8 Sham smoking consisted of the patient smoking an unlit cigarette for approximately one minute followed by a deliberate Mueller maneuver and finally two Valsalva maneuvers Note the lack of any significant change with the first two events followed by classical Valsalva responses Compare these last findings with Fig 1

found that smoking *two* standard cigarettes raised the arterial pressure by 21 1 mm Hg systolic and 13 0 mm Hg diastolic in 30 normal subjects and by 31 5 and 18 4 mm Hg in 56 subjects with essential hypertension The larger increases in arterial pressure in both their groups as compared with our subjects may simply reflect the fact that their patients smoked two cigarettes in succession in the resting state

One interesting observation was in Case 1 who developed angina pectoris following smoking a cigarette (Fig 4) This case has been discussed in detail elsewhere [15] The acute rise in arterial pressure coincident with the subjective appreciation of pain suggests a vasoreactive response which may have been triggered by reflexes resulting from local ischemia within the myocardium as reflected by ST segment depression occurring *before* the appreciation of pain or cardiovascular changes Alternatively, tobacco may raise the arterial pressure and heart rate to a level that precipitates cardiac pain the pain itself then producing a sudden rise in pressure as part of a generalized response

The results of our study in the completely unrestricted patient confirm a clear increase in blood pressure after smoking cigarettes The systolic rise in pressure was approximately twice that of the diastolic pressure and was present under different conditions of everyday life and demonstrates more clearly than laboratory studies the true pattern of events within the cardiovascular system during cigarette smoking Whether these changes of themselves contribute to the increased risk of arteriosclerosis and myocardial infarction associated with cigarette smoking remains problematic

Summary

Direct arterial pressure heart rate and ECG have been recorded over a 24 hour period in nine individuals who were completely unrestricted throughout the study Forty nine separate cigarette smoking episodes were clearly indicated and analyzed The results of our study confirm a significant increase in arterial pressure five minutes after smoking a cigarette The systolic rise in pressure (mean 10 7 mm Hg $P < 0\,001$) was approximately twice that of the diastolic rise (5 3 mm Hg, $P < 0\,001$) and was present under different conditions of everyday life with the notable exception of lying in bed before sleep We found no quantitative difference between normotensive and hypertensive subjects There was no certain change in heart rate (mean increase +0 8 beats per minute $t = 0\,59$ NS) in the group as a whole

Smoking also had a short term action consisting of a brief fall in arterial pressure and heart rate occurring over eight to ten heart beats

Table I Atrial pacing Wenckebach periods

A V ratio	No of patients	No of periods	Typical		Atypical	
			No.	%	No	%
4 3	24	55	38	69	17	31
5 4	17	29	4	14	25	86
6 5	12	18	2	11	16	89
7 6	9	12	0	0	12	100
8 7	4	4	0	0	4	100
9 8	4	4	0	0	4	100
10 9	1	1	0	0	1	100
11 10	2	2	0	0	2	100
12 11	—	—	—	—	—	—
13 12	—	—	—	—	—	—
14 13	1	1	0	0	1	100
15 14	—	—	—	—	—	—
16 15	—	—	—	—	—	—
17 16	2	2	0	0	2	100
Totals		128	44	34%	84	66%

Table II Spontaneous Wenckebach periods

A V ratio	No of patients	No. of periods	Typical		Atypical	
			No.	%	No	%
4 3	17	34	14	41	20	59
5 4	12	23	0	0	23	100
6 5	7	11	0	0	11	100
7 6	8	12	0	0	12	100
8 7	3	5	0	0	[illegible]	100
9 8	3	3	0	0	3	100
10 9	4	5	0	0	5	100
11 10	—	—	—	—	—	—
12 11	2	2	0	0	2	100
13 12	—	—	—	—	—	—
14 13	1	1	0	0	1	100
15 14	—	—	—	—	—	—
16 15	1	1	0	0	1	100
17 16	1	1	0	0	1	100
Totals		98	14	14%	84	86%

The following definitions were used (1) Wenckebach periods (WP) were defined as episodes of second degree block characterized by increasing P R or A H intervals from the first conducted beat of the period to that of any subsequent beat within the period, terminating in a dropped beat In all cases the first P R was shorter than the last P R (2) Typical Wenckebach periodicity was defined as the intermittent dropping out of a single ventricular beat associated with the following characteristics (1) progressive lengthening of the P R or A H interval (2) progressive shortening of the P R or A H increment (the change in successive P R or A H intervals) resulting in progressively decreasing R R intervals and (3) a pause which was less than any two P P intervals of consecutively conducted beats (3) Atypical Wenckeback periods were defined as those episodes which fulfilled the general definition of Wenckebach periods (see 1) but failed to meet all criteria for typical Wenckebach periodicity Wenckebach periods

The incidence of typical and atypical A-V Wenckebach periodicity

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Wenckebach originally described a form of conduction disturbance by noting a progressive lengthening of the interval between the a and c waves of the jugular pulse terminating in a dropped c wave[1] With the introduction of the electrocardiogram, Mobitz characterized the conduction disturbance as a progressive prolongation of the P R interval until there was a dropped ventricular beat (Mobitz type I block)[2] Wenckebach further characterized this phenomenon in a subsequent paper[3] He described the conduction disturbance as the intermittent dropping out of a single ventricular beat associated with (1) progressive lengthening of the P R interval, (2) the increment between the first and second conducted beats being the largest, (3) progressive decrease in R R intervals, and (4) a pause produced by the nonconducted P wave equal to the difference between the last P R (before the pause) and the first P R (after the pause) subtracted from twice the P P interval The term 'typical Wenckebach periodicity' has been applied to these characteristics Wenckebach and Winterberg[3] suggested that in the human heart departures from typical periodicity were frequent Other authors have also noted that the structure of a Wenckebach period can show significant variation from the classic pattern of typical Wenckebach periodicity[4-7]

The purpose of the present study was to quantitate the frequency of typical and atypical Wenckebach periodicity and to define the atypical variations in patients with spontaneous and pacing induced second degree A V block

Material and methods

Patients with Wenckebach periods (WP) both spontaneous and atrial pacing induced were studied to assess the frequency of typical and atypical Wenckebach periodicity All records were from patients seen at either the University of Illinois Hospital, the West Side Veterans Hospital, or Michael Reese Medical Center Tracings with atrial pacing induced periods were taken from records of patients undergoing diagnostic electrophysiologic studies Most of these patients were studied because of bundle branch block All of these patients had intact A V conduction during sinus rhythm His bundle electrograms were recorded using previously described techniques[8] The basic intervals were recorded during sinus rhythm, the atria were then paced slightly above sinus rate and then at increasing pacing rates (in steps of 10 beats per minute) until 1 1 conduction was lost and second degree A V block was observed

The second group consisted of patients with spontaneous Wenckebach periods determined from electrocardiographic rhythm strips The majority of these patients developed Wenckebach periods secondary to acute diaphragmatic myocardial infarction or digitalis excess Electrocardiograms with significant sinus arrhythmia were not analyzed

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Fig 2 His bundle recording of pacing induced atypical WP s Panels *A* to *D* show electrocardiographic Lead V_1 His bundle electrograms (HBE) and atrial electrograms (AE) from four different patients The arrows indicate pacing spikes H represents His bundle potentials A H intervals are listed in milliseconds Paper speed 100 mm per second. Panel *A* Shows atrial pacing at a cycle length of 380 msec with a Type II variant Note that the last A H increment is the largest of the period Panel *B* Shows atrial pacing at a cycle length of 545 msec with Type III variant Note that the same A H interval is repeated twice during the period. Panel C Atrial pacing at a cycle length of 360 msec with a Type IV variant Note that the A H interval decreases in the sixth conducted beat of the period. Panel *D* Atrial pacing at a cycle length of 465 msec with a Type V variant Note that the increment between the third and fourth conducted beats is larger than the first increment (25 msec) in the period.

Comparison of the pacing induced and spontaneous groups by chi square methods revealed a significantly higher incidence of atypical periods in the spontaneous group ($p < 0.01$) even though both groups demonstrated a high frequency of atypical WP The paced and spontaneous heart rates at which WP occurred had no influence on the percentage of atypical periodicity The incidence of typical WP did not differ significantly between those patients with normal A H (130 msec or less) and prolonged A H intervals during sinus rhythm.

Five categories of atypical WP were defined These were (1) last increment increased from the previous increment Figs 1 *A* and 2 *B* (2) last increment being the largest increment of the period, Figs 1 *B* and 2 *A* (3) P R (or A H) interval repeated at least once during the period, Figs 1 C and 2 *B* (4) P R (or A H) interval decreasing at least once during the period, Figs 1 *D* and 2 C, and (5) first increment not being the largest increment of the period Figs 1 *B* and 2 *D* It should be noted that any one WP could fit several of these categories.

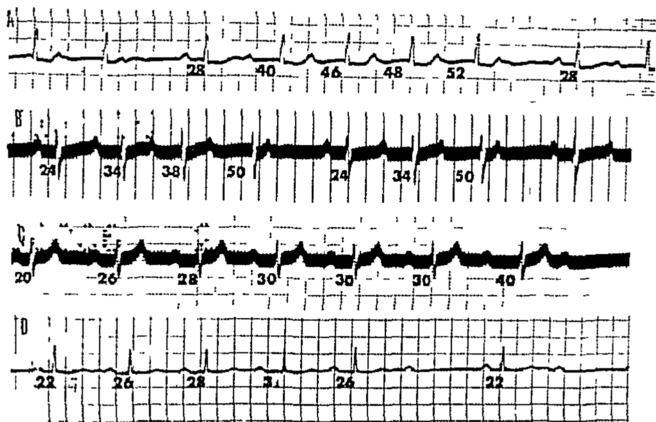


Fig 1 Electrocardiographic recordings of spontaneous atypical WP s. Panels *A* to *D* represent surface electrocardiographic Leads II obtained from four different patients P R intervals are listed in hundredths of a second Panel *A* Shows a Type I variant Note that the last P R increment increases from the previous increment Panel *B* Shows a Type II variant Note that the last increment is the largest increment of the period Panel *C* Shows a Type III variant Note that the same P R is repeated three times during the period Panel *D* Shows a Type IV variant Note that the P R interval decreased prior to the blocked P wave

(3 2) were not analyzed since these periods have only one increment and cannot be classified as typical or atypical

The first three consecutive paced Wenckebach periods were analyzed in each patient with His bundle recording All available recorded periods were analyzed from electrocardiograms of patients with spontaneous Wenckebach periods P R intervals were measured in the electrocardiographic records and A H intervals were measured in the cases with His bundle recordings Measurements were taken at 100 mm per second paper speed with His bundle recordings and at 25 mm per second paper speed with surface electrocardiograms P R intervals were measured to the nearest 0 02 sec and A H intervals to the nearest 5 msec The increment of change (Δ P R or Δ A H) in successive intervals was calculated from the interval measurements and listed Periods were then classified as either typical or atypical Atypical periods were further categorized to define the frequency of specific atypical features

Results

Tables I and II show the number of patients the number of WP analyzed, the number of typical and atypical WP and the A V conduction ratios at which these observations were made In 45 patients Wenckebach periods induced by atrial pacing were analyzed Of the 128 WP from these records 66 per cent were atypical and 34 per cent were typical There was a significant increase in the incidence of atypical periods as the length of the periods increased. Periods greater than 6 5 were all atypical The site of A V block in all the pacing induced WP was localized proximal to the His bundle (A V nodal)[9]

Electrocardiograms from 24 patients with spontaneous WP were studied None of the tracings showed major sinus arrhythmia Of the 98 periods from these patients 86 per cent were atypical while 14 per cent were typical There was again a significant increase in the percentage of atypical periods as A V conduction ratios (length of period) increased Periods greater than 4 3 were all atypical

tion of A V nodal conduction can result in unexpected changes in P R intervals A V nodal re entry and atypical WP s [14] Damato and co workers[15] in their study on the mechanism of the A V nodal Wenckebach phenomenon demonstrated the occurrence of both manifest and concealed A V nodal re entry during rapid atrial pacing Concealed A V nodal re entry could account for the occurrence of sudden prolongation of A V nodal conduction time prior to the blocked P wave [16] Changes in sympathetic and parasympathetic tone could also result in varying P R intervals and could account for the presence of atypical WP s [4, 17]

The present study does not define the mechanisms for the presence of atypical WP s but rather emphasizes the frequency of their occurrence In light of the observations presented in this study it becomes obvious that the typical Wenckebach period is the exception rather than the rule Thus we propose abolition of the terms typical and atypical since a close look at the structure of WP has shown that typical is atypical It should be pointed out that the 3 2 conduction ratio the most common variety of WP s cannot be classified as typical or atypical since there is only one increment present

Clinical implications The electrocardiographic diagnosis of S A and A V nodal exit Wenckebach second degree block depends on the assumption that these episodes will be characterized by typical Wenckebach periodicity [4] If atypical periodicity is as common with Type I exit block as it is with Type I second degree A V block then a considerable number of these exit blocks are never diagnosed. There is presently no means of diagnosing Type I S A and A V junctional exit block of greater than 4 3 conduction ratio unless characterized by typical Wenckebach periodicity

Summary

The classic pattern of the typical WP s consists of (1) progressive lengthening of the P R intervals with the largest increment occurring in the second conducted beat (2) progressive *decrease* in P R increment which accounts for the progressive shortening of successive R R intervals and (3) the pause produced by the nonconducted P wave is less than two P P intervals In 45 patients with atrial pacing induced Wenckebach periods of A V conduction the structure of these was studied with His bundle recordings Of the 128 periods analyzed exceeding 3 2 A V conduction ratios 66 per cent were atypical In 24 patients with spontaneous WP s of A V conduction the electrocardiographic records were studied. Of the 98 periods analyzed exceeding 3 2 A V conduction ratios 86 per cent were atypical WP s with A V conduction ratios greater than 6 5 were all atypical Five categories of atypical WP s are described.

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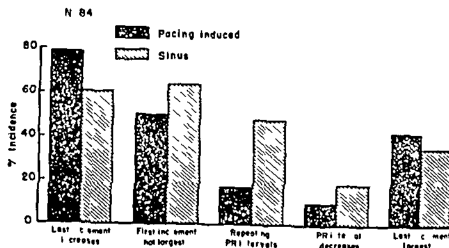


Fig 3 Frequency of variants in the spontaneous and pacing induced atypical WP s

Fig 3 shows the frequency of each of these categories for the pacing induced and spontaneous WP s The most frequent atypical finding was one in which the last increment increased This occurred in 79 per cent of the pacing induced and 61 per cent of the spontaneous WP s The last increment was in fact the largest increment of the period in 43 per cent of the paced atypical and 36 per cent of the spontaneous atypical periods

Discussion

Wenckebach in 1927 described electrocardiographic observation in Type I second degree A V block in which there was "lengthening of A V conduction time with periodic dropping of a ventricular systole whether produced artifically or observed at the bedside of a patient'[3] The electrocardiographic characteristics of this conduction defect were as follows (1) progressive lengthening of P R interval with the largest increment occurring between the first and second conducted beat (2) progressive decrease in P R increment resulting in decreasing R R intervals, (3) the pause produced by the nonconducted P wave is equal to the difference between the last P R before the pause and the first P R after the pause subtracted from twice the P P interval The term Wenckebach phenomenon or 'typical Wenckebach period has been applied when these characteristics are seen in electrocardiographic records In several reports it has been pointed out that spontaneous or pacing induced Wenckebach phenomenon can show significant variation from the classic pattern[4-7]

It has been our observation that typical Wenckebach periods are the exception rather than the rule We could not find a study designed to assess the frequency of typical and atypical Wenckebach periodicity in the literature The present study, with analysis of 98 spontaneous and 128 atrial pacing induced WP s demonstrated that 86 per cent of spontaneous and 66 per cent of pacing induced WP s were atypical There was a significant increase in the number of atypical periods as A V conduction ratios of WP s increased Periods with A V conduction ratio greater than 6 5 in both spontaneous and pacing induced WP s were all atypical There was no correlation between heart rate and the per cent incidence of atypical periodicity In the group with atrial pacing and His bundle recording the incidence of atypical WP s did not differ significantly between those with normal and prolonged control A H intervals Five categories of atypical WP s which had significant frequency were described The most frequent atypical finding was an increase in P R increment of the last beat prior to the dropped P wave The last increment was the largest in approximately one third of all atypical WP s

The mechanism of the Wenckebach phenomenon has not been entirely elucidated Microelectrode studies of the A V node in rabbit hearts have shown that conduction in the A V node is inhomogeneous[10] This inhomogeneity of conduction is further accentuated during rapid atrial pacing as shown by the cumulative effect of frequency upon excitability resulting in an increase in diastolic threshold and a temporal lag in recovery of excitability[11] Thus significant degrees in fractionation of the advancing wave front can occur Moe and Mendez[12] have demonstrated dissociation of A V nodal conduction into two functional pathways in the dog heart Work from our laboratory has shown similar dual A V nodal conduction in the human heart[13] Dissocia

ıows that ın the populatıon of the y the cases wıth supraventrıcular ȝ (SEB or AF) tended to have a hıgher lower $Paco_2$ than the cases wıthout thmıas

ıon existed between BBB and arterıal ses The presence of VEB was very ıssocıated wıth a low Pao_2 and hıgh The relatıon between VEB and arterıal ˏas analysıs ıs seen ın Fıgs 1 and 2 It nı...)e observed that VEB s were noted on 86 4 per cent of the routıne ECG s ın cases wıth a Pao_2 equal to or below 37 mm Hg whıle only 4 4 per cent of the cases wıth a hıgher Pao_2 showed VEB s Also VEB s exısted on the routıne ECG s of 68 4 per cent of the cases wıth a $Paco_2$ above 70 mm Hg but on only 19 5 per cent of the cases wıth a lower $Paco_2$

Sınce ın most occasıons a hıgh $Paco_2$ was assocıated wıth a low Pao_2 ıt ıs not obvıous from the above statıstıcal relatıons whether the ıncıdence of VEB s was dırectly related to hypercapnıa or hypoxıa the other relatıon beıng an ındırect one

Table IIIA shows the ıncıdence of VEB ın four groups separated accordıng to the presence of mıld or severe hypoxıa and hypercapnıa. From thıs table the total ıncıdence of VEB ın mıld (3/69) and severe (19/22) hypoxıa was calculated. If the 19 cases wıth severe hypercapnıa had a VEB ıncıdence determıned only by hypoxıa there should be $6 \times (3/69) + 13 \times (19/22) = 11\ 4881$ cases wıth VEB Sımılarly the expected number of cases wıth VEB ın the mıld hypercapnıa group should be $63 \times (3/69) + 9 \times (19/22) = 10\ 5119$ cases wıth VEB ıf theır ıncıdence ın mıld hypercapnıa group was determıned only by theır degree of hypoxıa The expected dıstrıbutıon of VEB ın cases wıth mıld and severe hypercapnıa (ıf the ıncıdence of VEB was determıned only by hypoxıa) was compared wıth the observed one (Table IIIB) usıng the X^2 method. The two dıstrıbutıons (observed and expected) dıd not dıffer sıgnıfıcantly from each other ($X^2 = 0\ 8273$ $P > 0\ 30$)

In a sımılar way the expected ıncıdence of VEB ıf determıned only by the degree of hypercapnıa was formed (Table IIIC) Thus from Table IIIA the total ıncıdence of VEB ın severe and mıld hypercapnıa was 13/19 and 9/72 respectıvely Sıx out of the 69 mıld hypoxıa cases had severe hypercapnıa and 63 cases had

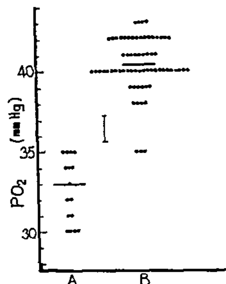


Fıg 1 Pao_2 ın cases wıth (*A*) and wıthout (*B*) ventrıcular ectopıc beats Horızontal lınes show the mean values Vertıcal lıne ındıcates the standard error of the dıfference of the means at a sıgnıfıcance level of 5 per cent

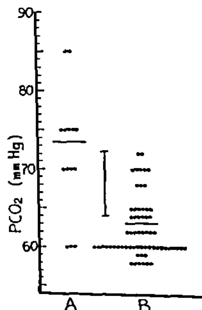


Fıg 2 $Paco_2$ ın cases wıth (*A*) and wıthout (*B*) ventrıcular ectopıc beats Horızontal lınes show mean values. The vertıcal lıne ındıcates the standard error of the dıfference of the means at a sıgnıfıcance level of 5 per cent

mıld hypercapnıa Consequently the expected number of VEB ın the 69 cases wıth mıld hypoxıa should be $6 \times (13/19) + 63(9/72) = 11\ 9802$ Thus the dıstrıbutıon of VEB ın the severe and mıld hypoxıa groups was calculated as expected, ıf the ıncıdence of VEB were determıned

Type of cardiac dysrhythmias in respiratory failure

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Estimates of the incidence of cardiac arrhythmias in cases of pulmonary disease vary considerably [1-4] The prognostic value of arrhythmias has recently been stressed Cases with ventricular arrhythmias have a grave prognosis [3] while the presence of any arrhythmia may aggravate the already existing tissue hypoxia by causing a reduction in cardiac output [4]

In spite of the obvious clinical importance of these observations no data exist on the causative relationship between respiratory failure and rhythm disturbances that might help in establishing the proper therapy

The purpose of the present study is to offer some information on the relation between the respiratory status, as judged by arterial gas analysis and the type of the dysrhythmia

Materials and methods

Ninety one patients (67 men and 24 women) form the material for this study They were selected among 324 patients who were admitted in this hospital with the clinical diagnosis of acute respiratory failure Every case admitted to the hospital with the above diagnosis had within one hour a routine 12 lead electrocardiogram (ECG) and an arterial blood gas estimation The 91 patients selected for the purpose of this study had some type of dysrhythmia on ECG and an arterial blood gas analysis with either a $Paco_2$ of $\geqslant 60$ mm Hg or a Pao_2 of $\leqslant 40$ mm Hg

The clinical diagnosis was bronchial asthma (38 cases) pulmonary emphysema (30 cases) and chronic bronchitis (23 cases) Their age varied from 25 to 82 years with a mean of 55 4 ± 3 1 (S E)

The blood sample for gas estimation was obtained from the femoral artery in heparinized syringes and immediately analyzed for oxygen tension (Pao_2) and carbon dioxide tension ($Paco_2$) in a Beckman gas analyzer Model 160

The study was retrospective and the cases were selected on the basis of the presence of the following arrhythmias supraventricular ectopic beats (SEB) atrial flutter and fibrillation (AF) ventricular ectopic beats (VEB) and complete right and left bundle branch block (RBBB and LBBB) Only the admission ECG s were taken into account. Approximately 60 cardiac cycles were recorded on each ECG The presence of sinus tachycardia (ST) over 100 beats per minute and sinus brachycardia (SB) below 60 beats per minute were also noted

Findings

The incidence of dysrhythmias observed is shown in Table I It may be seen that about 80 per cent of this highly select group of patients had some sort of supraventricular dysrhythmia (SEB or AF) The incidence of VEB in the routine ECG was 24 2 per cent The incidence of RBBB or LBBB was 20 9 per cent.

The Pao_2 values ranged from 28 to 44 mm Hg and the $Paco_2$ values ranged from 55 to 90 mm Hg

Table II shows the mean Pao_2 and $Paco_2$ values associated with the presence and the absence of each dysrhythmia examined as well as the mean age of each group

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Table IIIB

	Hypercapnia				
	Severe		Mild		
VEB	Observed	Expected	Observed	Expected	Total
Yes	13	11 4881	9	10 5119	22
No	6	7 5119	63	61 4881	69
Total	19		72		91

Table IIIC

	Hypoxia				
	Mild		Severe		
VEB	Observed	Expected	Observed	Expected	Total
Yes	3	11 9802	19	10 0198	22
No	66	57 0198	3	11 9802	69
Total	69		22		91

pressure [5] It is possible that in respiratory failure too while the genesis of ventricular arrhythmias is related to hypoxia the genesis of supra ventricular arrhythmias is related to an increased right atrial pressure rather than to arterial blood gases

The importance of the present findings may best be viewed on the basis of the data from other authors According to Hudson and co workers [3] ventricular arrhythmias bear a grave prognosis On the other hand, the observed close relationship between the severity of hypoxia and the incidence of VEB might be an indication that more generous oxygen administration than is usually supplied might improve the outcome of cases with severe respiratory failure This conclusion is similar to that of Holford and Mithoefer [4] according to whom the primary goal of treatment of chronic obstructive pulmonary disease should be the correction of hypoxia The present findings stress even more strongly the importance of the same goal in cases with respiratory failure

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Table I

Type of arrhythmia	Cases No	Cases Percent
Sinus tachycardia	28	30 8
Sinus bradycardia	4	4 4
Supraventricular ectopic beats	51	56 0
Atrial fibrillation or flutter	22	24 2
Ventricular ectopic beats	22	24 2
Left bundle branch block	6	6 6
Right bundle branch block	13	14 3

Table II

	Pa_{O_2}	P<	Pa_{CO_2}	P<	Age	P<
SEB	40 31		63 35		52 42	
		0 001		NS		0 02
No SEB	36 55		67 77		59 27	
AF	40 19		62 76		55 38	
		0 01		0 05		NS
No AF	32 20		66 47		55 21	
VEB	32 95		73 48		61 86	
		0 0005		0 0005		0 01
No VEB	40 44		63 09		53 38	
BBB	38 32		63 74		57 32	
		NS		NS		NS
No BBB	38 75		66 12		54 93	

only by the hypercapnia severity This expected distribution was statistically compared with the observed one (Table IIIC) using the X^2 method The difference between the expected and observed distributions was highly significant ($X^2 = 22\ 9507$, $P < 0\ 0005$)

The mean age of the cases with VEB s was significantly older than that of the cases without VEB s

Discussion

The incidence of several arrhythmias detected on the routine admission ECG was observed in a highly selected group of respiratory failure cases

The most important finding was a direct relation between the incidence of VEB s and the degree of hypoxia A PaO_2 of 37 mm Hg seems to be a critical value below which almost all cases (86 per cent) present VEB while the number of VEB cases at a PaO_2 above this value is negligible (4 per cent)

The observed relationship between VEB and hypercapnia was statistically shown to be inci

Table IIIA

Hypoxia		Hypercapnia Severe $Pa_{CO_2} > 70$	Hypercapnia Mild $Pa_{CO_2} \geqslant 70$	Total
	VEB	0	3	3
Mild	No VEB	6	60	66
$Pa_{O_2} > 37$	Total	6	63	69
	VEB	13	6	19
Severe	No VEB	0	3	3
$Pa_{O_2} \geqslant 37$	Total	13	9	22
	VEB	13	9	22
Total	No VEB	6	63	69
	Total	19	72	91

dental owing to the common co existence of severe hypercapnia with severe hypoxia The conclusions of Holford and Mithoefer[4] who found no relationship between the level of hypercapnia and the frequency and type of arrhythmias agree with those of the present study

Age could be another contributing factor for the genesis of VEB s

The absence of more severe ventricular arrhythmias like ventricular tachycardia in the present series is obviously attributed to the method used (selection on the basis of admission routine ECG)

An apparently odd finding in this study is the existence of less severe hypoxia and hypercapnia in cases with supraventricular arrhythmias (SEB and AF) than in cases without such arrhythmias The explanation of this finding may be found in the mode of selection of the patients The group without supraventricular arrhythmias consisted mostly of the cases with VEB s and consequently of cases with a very low PaO_2 Cases with neither supraventricular arrhythmias nor VEB s and with a high PaO or a low PaCO were excluded since only those with a PaO_2 ‹ 40 mm Hg or a $PaCO_2 > 60$ mm Hg were selected for this study

The only firm conclusion which may be drawn from the odd relationship between supraventricular arrhythmias and arterial gas analysis is that severe hypoxia or hypercapnia have not been shown to be causes for supraventricular arrhythmias in cases of respiratory failure In cases of mitral stenosis a statisticallly significant correlation has been observed between the incidence of AF and right atrial pressure while such correlation was not observed with left atrial

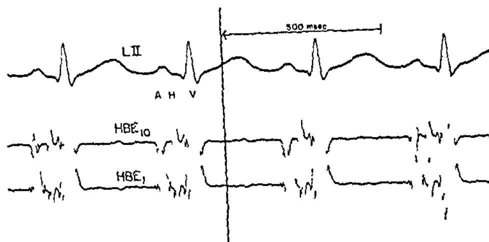


Fig 1 Normal His bundle electrogram (HBE) from a 10 month old child with a normal heart From top to bottom Lead II of the surface electrocardiogram HBE with 1 mm interelectrode distance and HBE with 11 mm interelectrode distance

cluded in the general statistics such as the success rate Many of these cases had undergone open heart surgery

Catheterization techniques Patients over two months of age were sedated with intramuscular meperidine hydrochloride (1 0 mg per pound) promethazine hydrochloride (0 25 mg per pound) and chlorpromazine (0 25 mg per pound) one hour before study The patient and all electrical equipment were securely grounded The catheter electrodes were connected to an Electronics for Medicine photographic recorder by way of a junction box Surface ECG s and IE were recorded simultaneously using frequency band widths of 0 1 to 20 Hz and 40 to 500 Hz respectively at paper speeds of 100 or 200 mm per second with one second time lines

Bipolar and tripolar electrode catheters (sizes 4 through 7 French) with interelectrode distances ranging from 1 mm to 10 mm were introduced through the femoral or saphenous vein In children over 10 pounds the percutaneous sheath technique was used,[8] while in smaller infants a saphenous vein cutdown was performed In a few cases HBE s were recorded from the left ventricle with electrode catheters introduced through a sheath previously placed in a femoral artery When necessary two electrode catheters were introduced percutaneously either into the same vein or into each of the femoral veins.

The electrode catheter was guided with fluoroscopy into the right ventricular apex and

Table I Cardiovascular defects in subjects with normal conduction by surface ECG

Normal structure and hemodynamics	19
Ventricular septal defect	15
D transposition of the great arteries	12
Patent ductus arteriosus	7
Pulmonic stenosis	7
Tetralogy of Fallot	7
Aortic stenosis	4
Atrial septal defect (secundum)	4
Coarctation of the aorta	3
Miscellaneous	7
Total	85

then slowly withdrawn with clockwise rotation until the His bundle deflection was seen on the oscilloscope (Fig 1) Several potentials were recorded sequentially in the low right atrium to ventricle (LRA V) interval but the potential following the low right atrial (LRA) deflection which was farthest from the ventricular electrogram was designated the HBP

In some cases, the HBP was recorded from the junction of the left ventricle and left atrium either with the catheter advanced across an atrial septal defect or patent foramen ovale or by placement of the catheter in a retrograde manner across the aortic valve or into the posterior sinus of Valsalva in the aortic root To record the high right atrial (HRA) potential the catheter

Intracardiac electrography in children and young adults

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Intracardiac electrograms (IE) recorded with electrode catheters are a useful adjunct to surface electrocardiography in the interpretation of conduction disturbances and arrhythmias in adults Giraud[1] was the first to record the His bundle potential (HBP) with catheter electrodes in humans he recorded unipolar electrograms in children with several forms of congenital heart disease Watson, Emslie Smith and Lowe recorded the HBP in one child with Ebstein s disease in 1967 using the same technique This technique was then modified and popularized in 1969 by Scherlag and others[3] who recorded bipolar His bundle electrograms (HBE) with band passage set at 40 and 500 Hz Several recent studies in children have found conflicting variations in the lengths of conduction intervals with age[4-7]

The purpose of this study was (1) to determine the normal intervals associated with conduction of the sinus node impulse to the ventricular myocardium in infants and children and changes in these intervals related to age and to compare these values with those measured in normal adults and (2) to study abnormalities of impulse formation and conduction in children with conduction disturbances and in patients receiving digitalis

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Methods

Patients The 158 *subjects studied ranged in* age from three days to 33 years and in weight from two to 70 kilograms These cases represent the first 158 consecutive attempts to record the HBP in our institution All but three subjects who were studied primarily for evaluation of arrhythmias underwent diagnostic cardiac catheterization for determination of an anatomic defect and hemodynamic abnormality

Normal group Included among the 158 patients studied were 85 (ages three days to 29 years) in whom the surface electrocardiogram (ECG) showed normal conduction Patients who had intracardiac surgery were excluded from this normal group Twenty two of the 85 patients were taking digitalis prior to the study none of these had clinical or electrocardiographic signs of toxicity nor were any of the patients receiving other medications known to alter conduction Digitalis was withheld for 24 hours prior to the study as part of the preparation for catheterization The cardiovascular lesions documented by cardiac catheterization in these 85 patients are listed in Table I

Abnormal group Of the 158 patients 43 with arrhythmias or conduction disturbances shown by surface ECG were evaluated to determine the effect of these abnormalities on the conduction intervals

The remaining 30 subjects could not be included into either the normal group or any of the specific groups of abnormalities being studied These subjects are therefore included in neither the normal nor the abnormal groups but are in

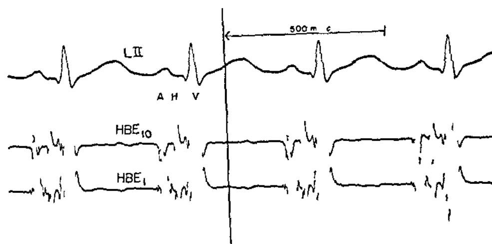


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Table II Mean intervals in subjects with normal conduction by surface electrocardiogram

Interval	Normal hemodynamics (19 patients)	Congenital heart disease 66 patients < 2 year old (21 patients)	2 10 year old (43 patients)	> 10 year-old (14 patients)
HR	107 ± 25	136 ± 23	109 ± 20	91 ± 20
PR	125 ± 18	124 ± 19	133 ± 19	130 ± 10
P LRA	14 ± 10	15 ± 12	18 ± 16	13 ± 12
LRA H	73 ± 17	72 ± 15	75 ± 19	79 ± 17
H V	38 ± 7	36 ± 8	41 ± 10	42 ± 11
Rb V	25 ± 7	24 ± 8	26 ± 10	28 ± 11

All intervals are the mean value in milliseconds ± 1SEM HR heart rate P beginning of P wave in surface ECG LRA low right atrium H His bundle Rb right bundle branch V ventricle

Table III Conduction abnormalities and arrhythmias studied in 43 subjects

First degree A V block	11
Second degree A V block	2
Third degree A V block	5
RBBB	18
Short PR	6
Premature beats	4
	46

was positioned at the junction of the superior vena cava and right atrium

Conduction intervals The intervals measured and their anatomic correlates are defined below

P LRA Beginning of P wave on simultaneously recorded surface ECG to first atrial deflection on the HBE This estimates the conduction time from the sinoatrial node to atrioventricular (A V) node

HRA LRA First rapid deflection on the HRA electrogram to first rapid deflection of the LRA electrogram This allows a more precise estimate of conduction from the area of the sinoatrial node to the area of the A V node than does the P LRA interval

LRA H First rapid deflection of LRA electrogram to first rapid deflection of HBP This represents conduction time through the A V node

H V First rapid deflection of HBP to the earliest ventricular activity either on surface ECG or IE This represents conduction time from the His bundle to the ventricular myocardium

Rb V First rapid deflection of a potential after the HBP to the earliest ventricular activity This represents conduction time from the right bundle to the ventricular myocardium

Results

The His bundle potential was identified in 156 out of 158 patients in whom this technique was attempted HBP s were recorded in virtually all congenital heart lesions including complex lesions such as transposition of the great arteries before and after surgical correction ventricular inverserion, tetralogy of Fallot endocardial cushion defects and tricuspid atresia as well as simpler lesions The right bundle branch potential and the right bundle to ventricle interval were also measured in 45 patients There were no complications

Normal group Table II lists the values for several conduction intervals determined from the IE in 85 subjects with normal conduction on the surface ECG Diagnostic catheterization confirmed the presence of a congenital cardiac defect in 66 of these subjects and proved the heart to be structurally normal in the remaining 19 subjects Statistical analysis of the conduction intervals by Student s t test showed no statistically significant difference between intervals measured in subjects with structurally normal hearts and in those subjects with congenital heart disease No statistical differences were found among the three age groups nor between the patients who had received digitalis and those who had not

Abnormal group The types of conduction abnormalities or arrhythmias found in the 43 subjects with abnormal surface ECG are listed in Table III

First degree A V block The conduction inter

Table IV Intervals in subjects with first degree atrioventricular block

Age (yrs)	*Diagnosis*	*HR*	*PR*	*QRS duration*	*P LRA*	*LRA H*	*H V*
			msec				
22/12	p/o VSD	107	175	120	0	135	40
2	T/F	100	210	90	0	180	30
18/12	Complex	125	160	95	35	105	20
2	ASD I	100	200	125	0	155	45
8	p/o ASD VSD	85	200	120	5	140	55
10	p/o ASD I	72	197	120	7	135	55
21	VI DILV	80	250	100	0	150	100
7	ASD I	109	200	115	30	135	40
12	p/o ASD I	110	175	110	30	70	75
4	T/F	133	200	90	30	100	70
5	p/o common ventricle	100	225	125	25	170	30

p/o postoperative VSD ventricular-septal defect T/F tetralogy of Fallot. ASD I, ostium primum atrial septal defect. VI, ventricular inversion. DILV double inlet left ventricle

Table V Intervals in subjects with pre excitation

Age	*Associated diagnosis*	*QRS*	*HR*	*PR*	*LRA H*	*H V*
				msec		
8 yr	Normal hemodynamics	120	83	110	95	15
8 yr	AS PS	110	80	105	100	0
2 mo	Left atrial rhabdomyoma	70	80	80	50	30
20 mo	Pompe s disease	80	129	90	35	30
2 yr	Normal hemodynamics	90	160	75	30	35
20 mo	VSD	80	100	100	55	35

AS aortic stenosis PS pulmonic stenosis VSD ventricular septal defect.

Table VI Intervals in subjects with right bundle branch block

Age (yr)	*Diagnosis*	*HR*	*PR*	*LRA H*	*H V*	*Rb V*
				msec		
12	p/o T F	83	170	115	55	10
3	PPH	58	140	100	40	—
4	p/o T/F	95	120	90	30	10
22/12	p/o VSD	107	175	135	40	—
8	p/o ASD VSD	85	200	140	55	—
17	p/o truncus	90	180	85	45	30
18	p/o VSD	85	150	80	45	—
4	p/o T/F	100	170	110	60	—
8	p/o truncus	95	150	125	55	—
33	p/o T/F	86	130	85	45	—
11	p/o T/F	80	105	60	50	—
4	p/o T/F	90	140	100	45	25
3	p/o DORV (dextrocardia)	105	115	75	35	25
12	p/o T/F	120	140	60	45	—
14	p/o VSD	83	170	90	45	—
6	p/o T/F	85	125	75	43	35
4½	p/o T/F	110	150	80	48	30
5	p/o common ventricle	100	225	170	30	10

p/o postoperative T/F tetralogy of Fallot. PPH primary pulmonary hypertension VSD ventricular septal defect ASD atrial septal defect. DORV double outlet right ventricle

vals measured in 11 subjects with first degree A V block none of whom were taking cardioactive drugs are shown in Table IV A prolonged LRA H interval was demonstrated in eight of the 11 subjects a prolonged H V interval in two subjects and prolongation of both intervals in one subject

Third degree A V block Congenital complete A V block was present in five of the 43 subjects with arrhythmias Three of these five subjects also had ventricular inversion in these cases, the block was found below the bundle of His potential In the fourth subject, the block was above the bundle of His In the fifth subject the site of block was in the bundle of His indicated by the occurrence of two separate His potentials (split His) one following atrial deflection and the other preceding ventricular depolarization (Fig 2)

Short P R interval Six subjects with short P R intervals were studied (Table V) Shortening of the H V interval was found in two subjects with QRS prolongation (Wolff Parkinson White syn

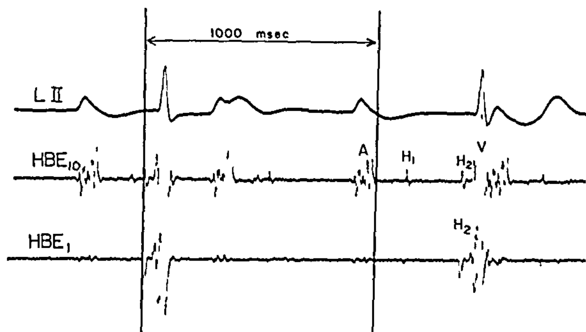


Fig 2 His bundle electrogram from a child with congenital complete heart block demonstrating a split His potential that is, His potentials following each low right atrial potential and before each ventricular electrogram indicative of block in the common bundle of His

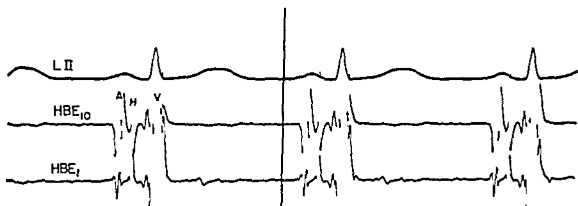


Fig 3 His bundle electrogram in a 20 month old child with a VSD short PR interval normal QRS and a history of tachycardia demonstrating shortened atrial to His bundle conduction consistent with atrioventricular node bypass

drome) and shortening of the LRA H interval was found in the four subjects with normal QRS duration and morphology (Fig 3)

Right bundle branch block The surface ECG indicated the presence of right bundle branch block pattern in 18 subjects none had associated left anterior hemiblock In 17 subjects the bundle branch block pattern had resulted from cardiac surgery The H V interval in all 18 cases was within two standard deviations of the normal mean The right bundle branch electrogram was identifiable in only seven cases the Rb V interval was normal in each of these cases (Fig 4)

Premature complexes or paroxysmal tachycardia IE were recorded in four subjects to investigate multiple premature complexes or paroxysmal tachycardia of obscure origin In one case both atrial and His bundle potentials were found before each premature complex indicating an atrial origin In another case only His potentials were identified and the H V intervals were 10 msec shorter than conducted beats indicating origin of the premature beats to be in a bundle branch In the third case no atrial or His potentials were recorded before the premature beats whereas they were recorded during comparable time before conducted beats showing the premature beats arose in the ventricular myocardium The fourth child had normal intervals both at rest and with multiple premature atrial con

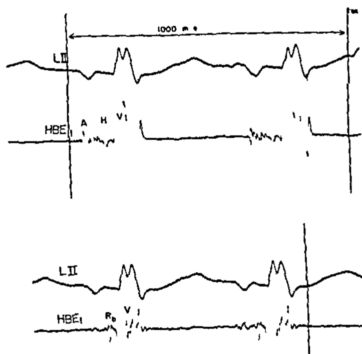


Fig 4 His bundle and right bundle branch potentials recorded in a three year-old after correction of double out let right ventricle with dextrocardia at which time a right bundle branch block pattern was induced on her elec trocardiogram

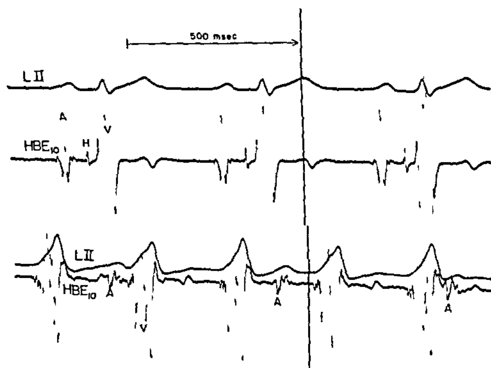


Fig. 5 His bundle electrograms from a six month old patient with recurrent tachycardia demonstrating normal intervals during sinus rhythm but no His potential during tachycardia

rnal



Fig 6 His bundle electrogram from a 12 year old girl six years after surgical correction of an endocardial cushion defect demonstrating a prolonged H V interval of 70 milliseconds.

tractions, but during a paroxysm of tachycardia no His potential could be found, indicating along with the A V disassociation and wide QRS complexes either ventricular tachycardia or nodal tachycardia with extra Hisian pre excitation (Fig 5)

The findings in the other 30 subjects were varied Twelve of the subjects had undergone Mustard operation and their conduction intervals were normal [14] Nine patients had ostium primum atrial septal defect and with the exception of those who had undergone surgery, the conduction intervals were also normal Studies were performed in two other subjects to delineate the type of A V block present following cardiac surgery One eight year old boy who had transient complete A V block after surgery to remove a subvalvular pulmonic stenosis associated with ventricular inversion had normal intervals 10 days after surgery The other subject with transient complete A V block postoperatively was studied six years after surgery because of syncopal attacks Despite a sinus rhythm this patient had a prolonged H V interval (Fig 6)

Discussion

Intracardiac electrography is useful in interpreting and treating certain obscure arrhythmias and conduction disturbances in adults [1-9] especially in determining the site and type of A V block, the localization of the focus for tachyarrhythmias and the type of accelerated A V conduction [10] Studies in children have been concerned with congenital heart block [11] surgical heart block,[12], Mobitz Type II block [13] and electrophysiologic abnormalities after Mustard operation [14] There are several reports of normal conduction intervals for adults and three reports of conduction intervals in children with congenital heart disease with and without abnormal surface ECG's [4-7] The effect of digitalis on conduction has not been studied in children

It is necessary to differentiate the right bundle branch potential from the HBP since confusing the HBP with the right bundle branch potential would give a falsely small value for the H V interval Other investigators have accomplished this either by His bundle pacing or by evaluating the response of the conduction intervals to right atrial pacing Neither of these methods are completely reliable and both introduce possible additional hazards to the patient i e, high milliamperage needed for His bundle pacing and additional catheter for atrial pacing We therefore used a different method to identify the His bundle potential We withdrew the catheter slowly across the tricuspid valve while recording The discrete rapid deflection in the LRA V interval preceding the ventricular electrogram by the greatest distance was identified as the HBP While the HBP was being recorded there was usually a large atrial electrogram This further helped to identify the HBP since the right bundle branch potential was usually accompanied by a small or absent atrial electrogram

Recording the HRA electrogram was found to be helpful in cases of A V dissociation and in studying internodal conduction The HRA LRA interval is almost always longer and less variable than the P LRA interval and is thus a more reliable measurement of internodal conduction The low amplitude of the P wave makes it subject to errors in measurement

The intervals found in this study in patients

with normal cardiovascular systems and in those with congenital heart defects with normal surface ECG s agree in general with the intervals reported by other authors Our findings differ from previous reports in that in our study statistical analysis of the conduction intervals showed no significant variation with age Of the previous three studies concerned with the influence of subject age on the intervals one found a statistically significant increase only in the A H interval the second, an increase only in the H V[5] and the third an increase with increasing age in both intervals studied[6] Since the premedications and techniques were similar it is surprising that such marked differences were found. Our study did not confirm an increase in the P R interval with increasing age under the conditions of our study We believe that the phenothiazine drugs used in premedicating children may shorten the P R interval through effects on autonomic tone and thus make it impossible to determine which interval increases with age Measurements made under these conditions however are useful in determining normal intervals in the cardiac catheterization laboratory setting where any detailed studies must take place

Our studies of conduction abnormalities indicate that there can be many different sites of block in patients with first degree A V block and that these sites can be identified definitely by analysis of IE Prediction of the site of all forms of atrioventricular block by surface ECG is less accurate in the child with congenital abnormality than in the adult with acquired disease Bundle branch block was not present in any of our patients with first degree A V block and a prolonged H V interval This is consistent with Rosen and co workers[15] who infrequently found a prolonged H V interval in subjects with right bundle branch block and first degree A V block

Whether the various sites of block have the same significance in infants and children as in adults remains to be seen however each of the patients with first degree A V block and prolonged H V interval had a defect known to predispose to complete A V block It is suspected that patients with first degree A V block and prolonged H V interval are prone to develop complete A V block Prolongation of the P LRA and LRA H intervals in adults has been said to have a more benign prognosis this study has produced no evidence to contradict this in children

Our findings in the subjects with accelerated A V conduction agree with studies of adults with this condition in that the QRS morphology is a good predictor of the type of pre excitation

The conduction intervals in 85 children and young adults with normal conduction by ECG were found to be the same as previously reported for adults and contrary to previous reports did not vary significantly with age The technique of His bundle recording in children was found to be safe and informative in the study of conduction disturbances and arrhythmias in congenital heart disease arrhythmias of obscure origin and localization of the site of heart block The prognostic value of localizing the site of A V block in children with IE can be determined only after longer follow up of these patients

Summary

The interpretation of IE recorded in children has been hampered by a lack of agreement regarding normal values We recorded IE in 158 children and young adults (ages three days to 33 years) to define the various conduction intervals in normal and disease states The HBP was recorded in 156 subjects In 85 subjects with normal conduction indicated by surface ECG including 19 subjects with normal hearts, there were no statistically significant age related differences in internodal A V nodal or His Purkinje conduction intervals Therapeutic levels of digitalis did not alter the conduction intervals

In 11 subjects with first degree A V block and in five subjects with congenital complete A V block the site of block as determined by IE could not be predicted from the surface ECG No abnormalities in conduction intervals were found in 18 subjects with right bundle branch block (surgically induced in 17 cases) Intracardiac electrography with recording of the HBP was found to be a safe informative technique for electrophysiologic investigations in children and young adults

We would like to acknowledge the technical assistance of Mr Fidel Elizondo and Mr Konrad Kail the editorial assistance of Mrs Ellen Erwin, and the secretarial assistance of Miss Nan O Keeffe on this paper

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Fig 6 His bundle electrogram from a 12 year old girl six years after surgical correction of an endocardial cushion defect demonstrating a prolonged *H V interval of 70 milliseconds*.

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The intervals found in this study in patients

Experimental and laboratory reports

Electrical alternation of the T-wave Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome

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Milan, Italy

Since Mines s report in 1913 [1] it is well known that alternation of the T wave in amplitude or in polarity unaccompanied by changes in the QRS complex may be present in electrocardiographic (ECG) tracings This intriguing phenomenon which is rare in clinics [2] has also been observed in some experimental conditions[1,3-10] but nearly always as an unexpected event Presently its meaning is still regarded as obscure

The observation of episodes of electrical alternation of the T wave in a patient affected by the long Q T syndrome (Romano Ward type) led us to examine from this point of view all the articles concerning this severe illness Surprisingly we found that T wave alternans was present although often not recognized or discussed, in thirteen[11-23] out of 28 reports [11-38] which is striking when compared to the very limited number of such observations in patients with other diseases [39-45]

We were further impressed by observing that in patients with the long Q T syndrome T wave alternans usually occurred during stresses since there is a growing evidence of a relationship of this syndrome with the sympathetic nervous system Stimulation of the left stellate ganglion for instance prolongs the Q T interval in dogs [46]

It also seemed reasonable to postulate some relation between the alternation of the T wave and the sympathetic nervous system Attempting an experimental approach we found that alternation of the T wave could be obtained by stimulating those same cardiac sympathetic nerves which can induce a prolongation of the Q T interval

A preliminary account of this work has been presented [47]

Case report

In January 1971 a 9 year old girl A B was referred to us because of frequent (3 to 4 times a week) syncopal attacks. The episodes had begun when she was three years of age they usually lasted one or two minutes during which time she was unconscious apneic and pulseless The precipitating cause was either a physical effort or a violent emotion like anger or more commonly sudden fright

An older sister C B had suffered from similar episodes since she also was three years of age She died suddenly when she was 19 years of age as a consequence of violent emotion while she was part of a live audience for a television program The postmortem examination revealed no abnormal findings and her death remained unexplained.

The physical examination and chest x ray of our patient (A B) revealed no abnormalities All laboratory investigations including measurement of potassium and calcium in both serum and urine were normal The ECG (Fig 1 *A*) showed a greatly prolonged Q T interval (Q T c 0 61) The audiogram was normal

This urged us to recuperate an ECG of the older sister (C B) performed a few months prior to her death the Q T interval was also prolonged (Q T c 0 50)

A study of the family revealed that the parents were cousins The patient s maternal grandmother mother and two out of five brothers had a Q T interval at the upper limit of normal values or slightly prolonged (Q T c from 0 43 to 0 46) but no syncopal attacks were reported.

Therefore our patient (A B) was diagnosed as having the long Q T syndrome (Romano Ward type) It was also clear that the same illness had caused the death of her sister

During hospitalization in order to perform an *exercise* test we brought the patient to the exercise room where she was frightened by the unusual apparatus (treadmill polygraph oscilloscope etc) An ECG recorded at that moment showed a clear alternation of the T wave (Fig 1 *B*) which lasted for several minutes. On two other occasions the same phenomenon was observed after exercise tests

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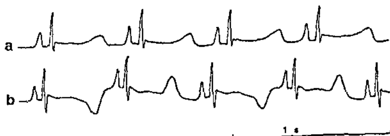


Fig 2 Anesthetized cat ECG (D2) A, Control B 5 sec after the cessation of a 30 sec electrical stimulation of both stellate ganglia (left ganglion 20 V 2 msec and 20 Hz right ganglion 10 V 2 msec and 20 Hz) Alternation in polarity of the T wave is evident

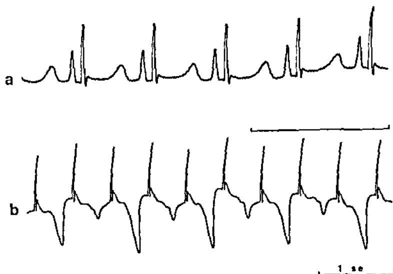


Fig 3 Anesthetized cat ECG (D2) A Control B 3 sec after the cessation of a 30 sec electrical stimulation of the decentralized left stellate ganglion (20 V 2 msec and 20 Hz) Alternation in amplitude of the T wave and nodal rhythm are manifest

(Figs 3 B and 5 B and C) while in others the polarity was changing as well (Figs 2 B and 5 A) However these are not two different types of alternation[7] since in some cases they were both observed in the same lead during different periods of the same episode (Fig 4)

Simultaneous recording of arterial blood pressure indicated that T wave alternans was always associated with mechanical alternation (Fig 5) as revealed by the presence of pulsus alternans Arterial systolic pressure during pulsus alternans always varied by less than 10 mm Hg

Alternation was obtained in about 30 per cent of the experiments. In some of them it was reproduced in each trial in others it could only be evoked a few times.

Heart rate increases accompanying T wave alternans were usually modest (10 to 20 beats per minute) In a few cases the heart rate was not affected at all the stimulation being restricted to the left stellate ganglion[53]

Discussion

Alternation of the T wave This phenomenon consists of the rhythmic alternation of the configuration of the T wave without any concomitant change in the QRS complex T wave alternans lasting a few cardiac cycles may be observed following a premature beat[58,59] However the clinical and experimental findings reported in this paper do not represent postextrasystolic phenomena

In animal experiments T wave alternans has been observed associated with quite different conditions such as occlusion of a coronary ar

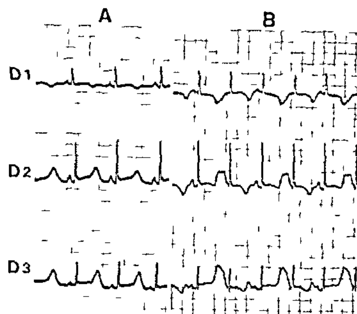


Fig 1 (A B) A Control condition QT c 0 61 B During fright Tracings in B are simultaneous Alternation of the T wave in amplitude (D1) and in polarity (D2 and D3) is evident

The girl was placed under treatment with a beta blocking agent (propranolol 160 mg a day) during the next two years a valuable degree of protection was clearly exerted by the drug since she had only six syncopal attacks. However considering that any of these episodes could be fatal this therapy could not be regarded as sufficient

On the basis of the successful surgical attempt reported by Moss and McDonald[22] and of the experimental data obtained by Yanowitz Preston and Abildskov[46] and ourselves (see below) surgical treatment seemed rational

In March 1973 A B was operated on part of the left sympathetic chain was removed (comprising the inferior half of the stellate ganglion and the second and third thoracic ganglia) This type of sympathectomy did not produce a Bernard Horner syndrome The Q T interval became slightly shorter but is still far from normal Nonetheless the patient has remained free of syncopal attacks since then although she accomplished severe physical efforts for the first time in her life It is however too short a period of time from which to draw any conclusions on the real value of this surgical therapy For sake of safety medical treatment has not yet been discontinued

Methods

Experiments were performed on cats which were anesthetized with Nembutal (35 mg per kilogram intraperitoneally) The animals were paralyzed with gallamine triethiodide and ventilated artificially The guidelines of the American Physiological Society regarding anesthetized curarized animals were followed Polyethylene catheters were introduced in a femoral vein and artery Both vagi were cut in the neck

In some experiments the left stellate ganglion was exposed retropleurally[48,49] and prepared for electrical stimulation In other experiments the chest was opened to expose both stellate ganglia[50] for simultaneous electrical stimulation in these cases the central connections of the ganglia represented by the first four thoracic rami communicantes[51] were severed

Bipolar platinum electrodes were connected through isolation units to Tektronix stimulators (Series 160) Pulses were generally 5 to 20 V 2 msec, and 10 to 31 Hz they were usually maintained for 5 to 30 sec periods The current passing through the electrodes was calculated by measuring on an oscilloscope the voltage drop across a 10 Ω resistor placed in series

Recording procedures for arterial blood pressure ECG, and heart rate directly or on tape have been described previously[49,50]

Results

In 11 experiments alternation of the T wave was induced by electrical stimulation of one or both stellate ganglia When both ganglia were stimulated simultaneously alternation could only be obtained (three experiments) when a more intense stimulation was applied to the left stellate ganglion (Figs 2 B 4 B through F and 5, A)

Unilateral stimulation was successful only when applied to the left stellate ganglion (eight experiments) In five of these experiments the rami communicantes of the ganglion were severed (Figs 3 B and 5 B and C) in three other experiments they were left intact.

Electrical stimulation also produced the well known effects on ECG heart rate and blood pressure[46,52-54]

It should be recalled that supramaximal electrical stimulation of a stellate ganglion also excites those afferent nerve fibers which run through it[51] part of them having their sensory endings in the heart[49,55] are known to mediate sympathetic reflexes distributed back to the heart[50,56,57] Thus when the intact left stellate ganglion was stimulated the increased sympathetic activity directed to the heart was elicited both directly and through reflex mechanisms involving the right stellate ganglion[50,57]

Alternation of the T wave developed after stimulations lasting for 5 to 30 sec and could persist for 20 to 30 sec after cessation of the stimulus In some cases it affected the amplitude of the T wave without a reversal of its polarity

ablation of the right stellate ganglion or the electrical stimulation of the left one Since stellate stimulation shortens the recovery time that finding was rather unexpected.[62] However it was well explained by the cancellation theory [63]

Our experiments indicate that sympathetic stimulation can elicit not only a prolongation of the Q T interval but also T wave alternation

This phenomenon did not constitute a mere ECG feature since it was always associated with pulsus alternans It is likely that this is what occurs in clinics as well where the modest variations in pulse pressures may be easily overlooked

Clinical implications The occurrence of T wave alternation episodes in various experimental and clinical conditions suggests that several different mechanisms may be involved in this phenomenon Among these mechanisms abrupt increases in sympathetic activity are likely to play a major role in the course of a normal life

Since patients with long Q T syndrome seem to have a clear tendency to develop episodes of T wave alternans under emotions of physical stresses we suggest that this fact should be considered as a part of the syndrome

We should finally remember that other pathologic states such as cerebrovascular accidents [64] can be characterized by ECG abnormalities which are thoroughly mediated by the visceral nervous system

Summary

In a patient affected by the long Q T' syndrome we observed episodes of alternation of the T wave associated with emotional or physical stresses.

In anesthetized and vagotomized cats we could reproduce both the lengthening of the Q T interval and episodes of alternation of the T wave by electrical stimulation of the left stellate ganglion Our experiments provide further support on the relationships between the long Q T syndrome and the sympathetic nervous system and indicate that alternation of the T wave may depend on abrupt increases in the sympathetic discharge

We thank Dr M Periti for his assistance during the experiments and Dr A Guareschi for referring the case

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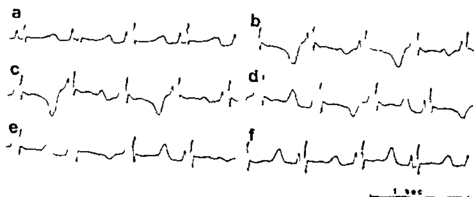


Fig 4 Anesthetized cat. ECG (D2) *A Control B* 6 sec after a 30 sec simultaneous stimulation of both stellate ganglia (left ganglion 20 V 2 msec and 20 Hz right ganglion 10 V 2 msec and 20 Hz) *C* 1 sec after the end of *B D* 4 sec after the end of *C E* 1 sec after the end of *D F* 2 sec after the end of *E* It is evident that the alternation in polarity of the T wave gradually evolved in an alternation in amplitude

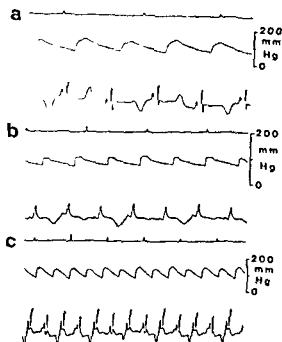


Fig 5 Anesthetized cats Tracings from top to bottom are time in seconds femoral arterial pressure ECG (D2) *A* 19 sec after the cessation of a 20 sec stimulation of both stellate ganglia (left ganglion 20 V 2 msec and 31 Hz right ganglion 10 V 2 msec and 25 Hz) *B* 5 sec after the cessation of a 25 sec stimulation of the decentralized left stellate ganglion (12 V 2 msec and 31 Hz) *C* 2 sec after cessation of a 20 sec electrical stimulation of the decentralized left stellate ganglion (20 V 2 msec and 20 Hz) Alternations of the T wave are associated with pulsus alternans the lower arterial systolic pressures corresponding to the cycles with a larger Q T interval

tery,[3,4,7] increases in circulating catecholamines[8] and hypocalcemia[9,10] In some clinical reports it was also associated with hypocalcemia[10,39,44] We noticed that it was particularly frequent in patients affected by the 'long Q T syndrome

Long Q T syndrome The association of a long Q T interval congenital deafness, and syncopal attacks due to ventricular fibrillation following emotional or physical stresses is a clinical entity known as the *Jervell Lange Nielsen syndrome* Absence of the congenital deafness characterizes the otherwise identical Romano Ward syndrome *Both conditions (long Q T syndrome)* have a very high mortality rate and undoubtedly contribute to sudden death in children[60] The continuously growing number of reports moreover, suggests that this illness is much more frequent than previously suspected

The pathogenesis of the long Q T syndrome is still unknown although a number of hypotheses have been advanced including abnormalities of sinus node vascularization[61] myocardial metabolism[19,24,25] and effects of adrenergic stimulation[02,61]

In patients with this syndrome the prolongation of the Q T interval represents a rather stable feature while alternation of the T wave seems to be related to an abrupt increase in sympathetic activity

Moss and McDonald[22] reported that pharmacologic blockade of the right stellate ganglion in a patient with long Q T syndrome resulted not only in the predictable[46] lengthening of the Q T interval but unexpectedly also resulted in alternation of the T wave Their intervention probably caused a sudden imbalance between the sympathetic discharges reaching the heart from left and right stellate ganglia It is striking that the experimental conditions under which we obtained alternation of the T wave were similarly characterized by an asymmetrically increased discharge from the left stellate ganglion

Sympathetic stimulation *Yanowitz Preston* and Abildskov[46] found in the dog that a prolongation of the Q T interval follows either the

Influence of perfusion pressure and heart rate on local myocardial flow in the collateralized heart with chronic coronary occlusion

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It has been shown in man as well as in experimental animals that severe coronary stenosis and occlusion can be compensated by the development of a collateral circulation [1 3] Collaterals have unquestionably a protective value which in some cases totally prevents cardiac muscle necrosis [3] However many patients with known coronary artery disease partly compensated by collaterals suffer from anginal attacks and others develop myocardial infarction without acute thrombosis Disturbances in local myocardial perfusion aggravated by unfavorable hemodynamic conditions are discussed as triggering events which may lead to myocardial infarction even without acute thrombosis but in the presence of old coronary lesions partly compensated by collaterals [4]

Observations from our laboratory[5] have recently shown that multiple chronic experimental coronary occlusions can be tolerated without myocardial infarction provided the speed of arterial narrowing is sufficiently slow for the collaterals to develop

We have furthermore shown that forced hemodynamic changes produce disturbances in the local myocardial microcirculation in these hearts [6]

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The present study is an attempt to quantitatively describe the magnitude of these perfusion disturbances by means of classical pressure flow relations

A functionally and anatomically well defined compartmentation of myocardial perfusion was found which explains certain clinically known observations and which aids understanding of vascular regeneration in experimental ischemic heart disease

Methods

The experiments were carried out in 44 mongrel dogs of either sex of unknown age with an average body weight of 21 kilograms The dogs were divided into three groups (1) a control group of ten normal dogs (2) a group of dogs which were studied four weeks after implantation of two Ameroid constrictors on the coronary arteries and (3) a group of dogs which were studied five months after implantation of the Ameroid constrictors

Surgical procedures Thirty four dogs were operated upon under sterile conditions during anesthesia with piritramide [7] 2 5 mg per kilogram subcutaneously and sodium pentobarbital 15 mg per kilogram intravenously For artificial respiration a Bird Mark 7 was used. A thoracotomy was performed through the fourth left intercostal space and the heart was suspended in a pericardial cradle

Ameroid constrictors of appropriate size were slipped over the circumflex branch of the left

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Table I Mean values of the experimental data comparison of the control conditions and maximal vasodilation in the different groups of animals

	LAD flow (ml./min. 100 Gm.)				*LC or collateral flow (ml./min. 100 Gm.)*								
	Tot	*Epi*	*Endo*	*Endo/Epi*	*Tot*	*Epi*	*Endo*	*Endo/Epi*	*AvD (vol %)*	*MVO*	*HR*	*AoPm*	*LV dp/dt max*
Group A													
Normal dogs Control	71	59	81	1 40	68	56	76	1 44	15 9	11 3	72	117	2 900
Maximum Vasodilation	451	392	476	1 24	469	410	481	1 19	3 5	15 2	109	99	3 800
Group B													
Four weeks DC Control	59	47	68	1 44	53	44	58	1 34	12 6	7 0	77	99	3 000
Maximum Vasodilation	257	165	330	2 05	135	158	111	0 72	5 6	—	90	105	2 800
Group C													
Twenty weeks DC Control	78	68	85	1 32	74	76	78	1 23	15 2	13 3	68	109	2 200
Maximum Vasodilation	583	517	546	1 11	319	372	250	0 68	3 1	—	92	100	3 100

LAD flow blood flow to the area uppli d by the left ant rior d sc d ng c ronary artery
LC or collate al fl w blood flow to the ea suppl ed by the c umfl x branch of the left coronary artery or by collaterals
tot. total blood flow to th pecti e a ea
ep blood flow to th ep c d al l yers
end blood flow to the endoc di l layers
end ep tio of th blood fl w to the endocard um and the epicardium
AVD differ ce in oxygen c nt t n arterial a d coronary sinus blood.
MVO2 oxyg n consumption f th myocardium ml. O_2 pe minut 100 g
HR heart te
A Pm mea rtic pressur
LV dp dt max. ma mal dp/dt of th l ft entricul pr sur

Table II Mean values of the experimental data comparison of maximal vasodilation and vasodilation plus pacing in Group A and Group B The same abbreviations were used as in Table I

	LAD flow (ml./min 100 Gm.)				*LC or collateral flow (ml.min. 100 Gm.)*								
	Tot	*Epi*	*Endo*	*Endo/Epi*	*Tot*	*Epi*	*Endo*	*Endo/Epi*	*AvD (vol. %)*	*MVO_2*	*HR*	*AoPm*	*LV dp/dt max*
Normal dogs maximum vasodilation	451	39[illegible]	476	1 24	469	410	481	1 19	3 9	15 2	109	99	3 800
Normal dogs maximum vasodilation pacing	36[illegible]	364	336	0 99	371	369	331	0 99	6 1	22 3	203	98	3 050
Four weeks DC maximum vasodilation	273	191	336	1 99	137	163	111	0 69	4 5	—	107	99	3 200
Four weeks DC maximum vasodilation + pacing	231	197	254	1 33	113	164	71	0 43	6 4	—	211	99	2 550

coronary artery and the right coronary artery close to their respective origins The chest was closed in layers and the dogs were allowed to recover

Experimental procedures Acute experiments were carried out in all animals of all groups under anesthesia with piritramide 5 mg per kilogram subcutaneously and sodium pentobarbital 10 mg per kilogram intravenously Anesthesia was maintained with 80 + 20 nitrous oxide oxygen under intermittent positive pressure respiration with a Bird Mark 7 Mark 4 combination Aortic blood pressure was measured via a 7 F Cournand catheter (brachial artery) connected to a Bell & Howell pressure transducer Left ventricular pressure and its time derivative (dp/dt) were measured with a 5 F Millar type catheter tip manometer (femoral artery) and an active RC circuit The variables including Lead II of the electrocardiogram (ECG) were recorded on a Siemens Oscillomink ink jet recorder For coronary sinus sampling an 8 F Goodale Lubin catheter was advanced via the jugular vein into the coronary sinus under fluoroscopic guidance A short Cordis pigtail catheter was placed in the left ventricle via the left carotid artery for injection of radioactive tracer microspheres (TM) For electrical stimulation of the heart a USCI pacing catheter was placed into the right ventricle (via jugular vein) and connected to a Grass S 88 stimulator Arterial and coronary venous oxygen content was measured using a Lex O_2 Con oxygen analyzer Hemoglobin was determined with an Eppendorf cuvette spectrophotometer and the hematocrit was measured by centrifugation of blood filled micropipettes

Tracer microspheres (TM) Regional myocardial blood flow was measured with the TM technique Five different isotopes were used I 125 Ce 141 Cr 51, Sr 85, and Nb 95 I 125 and Nb 95 labeled beads had a diameter of 15 μ the others were 8 to 10 μ The problem of TM aggregation was solved by adding benzalkonium 0 05 per cent, and heparin to the suspension and by ultrasound deaggregation with a Branson B 12 Sonifier before every injection Approximately two million beads were injected for every blood flow determination The TM data (counts per minute per milligram of tissue) were calibrated to milliliters per minute per one hundred grams of tissue by the reference sample method of Makowski and co workers [8] Buckberg and co workers,[9] and Domenech and co workers [10] For this purpose, a wide bore catheter was placed into the terminal aorta via the femoral artery and connected to a Gilford constant speed withdrawal pump at 22 ml per minute After the experiment, the animals were killed by an overdose of sodium pentobarbital, the heart was removed and fixed in phosphate buffered 4 per cent formaldehyde for two days The atrial cap was removed and the ventricles were sliced perpendicular to the apex base axis with a calibrated sausage slicer From each slice the left ventricle was isolated from the right and further divided into four areas (1) the interventricular septum (2) the part of the anterior free wall characterized by the prominence of the anterior papillary muscle and perfused by the anterior descending branch of the left coronary artery (LAD) (3) the part of the posterior free wall characterized by the prominence of the posterior papillary muscle and supplied by sub branches of the circumflex branch of the left coronary artery (LC) in normal dogs and by collaterals in dogs with chronic coronary occlusions and (4) the part of the free wall in between 2 and 3 and supplied by both sub branches of the left anterior descendens and the left circumflex coronary artery

Areas 1 and 4 were discarded in this study to get a clear separation between myocardium exclusively supplied by the LAD and myocardium supplied only by the left coronary in normal dogs and by collaterals in dogs with chronic coronary occlusions The tissue blocks originating from areas 2 and 3 were further divided into an epicardial endomural and endocardial sample Each sample was accurately weighed coded and transferred to disposable plastic test tubes The tubes were automatically transported by a Selektronic sample changer into and out of a three inch Na I well type scintillation crystal The transport was controlled by a ND 812 8 K 12 bit process computer The compound gamma spectrum of the five radionuclides, present in the tissue samples was analyzed by the ND 812 process computer Background correction and spillover produced by the Compton scattering were taken into account Details of the computer program have been published elsewhere [6] Corrected activities were expressed as counts per minute per milligram The data were printed out on a teletype printer and punched in parallel on paper tape The paper tape was fed into an IBM

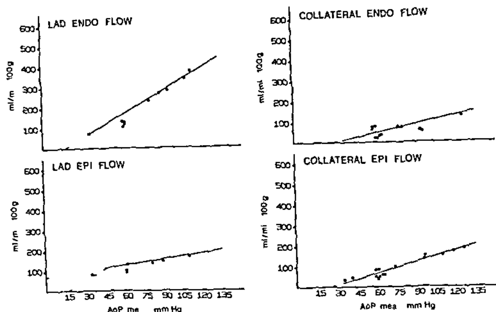


Fig 2. Pressure flow relations during maximal vasodilation in the different myocardial areas in dogs with chronic coronary artery occlusions The left panel represents the pressure flow relations in the endocardial (top) and epicardial (bottom) layers of the myocardium supplied by the patent anterior descending branch of the left coronary artery The dotted line starting at 15 mm Hg in the LAD epicardial curve represents the hypothetic course of the curve at low pressure levels (for explanation see text) The right panel shows the pressure flow relationships in the endocardial (top) and epicardial (bottom) layers of the myocardium supplied by collaterals

ble scar in the posterior papillary muscle and two of them had a supplementary right ventricular aneurysm All animals with a myocardial infarction were discarded from the study Ten of the remaining 18 animals were studied four weeks postoperative (Group B) and the eight others five months postoperative (Group C)

Regional coronary flow in control conditions The regional coronary flow pattern was homogeneous in every group Only the flow to the endocardial layers was slightly higher than to the epicardial ones In the normal animals calculated mean oxygen consumption was 11 3 ml per minute 100 Gm In the double constrictor group four weeks after implantation (Group B) oxygen consumption was significantly lower ($p < 0.05$) (7 0 ml per minute 100 Gm) while five months after operation (Group C) the oxygen consumption at rest was again in the normal range (13 3 ml per minute 100 Gm) and not significantly different from the controls (see Table I)

The mean values for aortic pressure heart rate and left ventricular dp/dt are summarized in Table I The small differences between the respective groups are not statistically significant

Regional coronary blood flow during maximal dilation The pressure flow relationship during maximal vasodilation in normal dogs is presented in Fig 1 This relationship is linear for both epicardium and endocardium Both curves have their intercept with the pressure axis around 20 mm Hg The flow increase to the endocardium was little but not significantly ($p > 0.05$) higher than to the epicardium When the mean aortic pressure was within a normal physiologic range (100 mm Hg) the flow went up to 400 to 450 ml per minute 100 Gm Under these conditions oxygen consumption rose significantly ($p < 0.05$) to 15 2 ml per minute 100 Gm (1 35 times control) Also LV dp/dt max increased significantly ($p < 0.05$) in comparison with control from 2 900 mm. Hg per second to 3 800 mm Hg per second (1 31 times control) Also a small increase in heart rate and a little fall in blood pressure was noted during maximum dilation in comparision with the resting condition (see Table I) Four weeks after implantation of two ameroid constrictors the pressure flow relation of the endocardial LAD area is still a linear function and quite comparable with that of normal dogs (see Fig 1 and 2) The epicardial LAD flow on the other hand, behaves completely different ($p < 0.05$) When the perfusion pressure

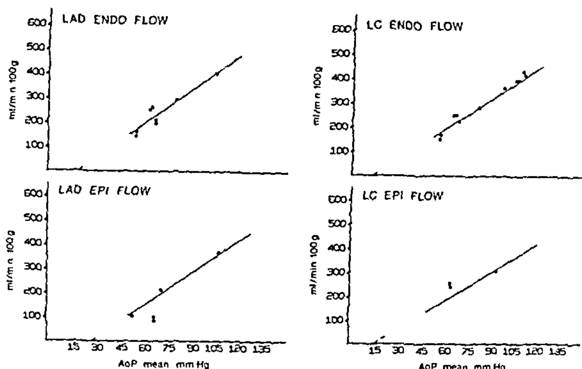


Fig 1 Pressure flow relations during maximal vasodilation in different myocardial areas in normal dogs The left panel represents the pressure flow relationship in the endocardial (top) and epicardial (bottom) layers of the myocardium supplied by the anterior descending branch of the left coronary artery The right panel represents the same for the myocardium supplied by the circumflex branch of the left coronary artery

130 computer for graphic presentation via Calcomp plotter

Statistical significance was accepted at the 5 per cent probability level when using the student t test.

Design of the experiment After a control period of approximately 15 minutes when all he modynamic variables were stabilized the first TM injection was made Simultaneously arterial and coronary sinus blood was withdrawn and ox ygen content was determined Aortic pressure left ventricular pressure left ventricular dp/dt and ECG Lead II were recorded continuously Dipyridamole 0 5 mg to 1 0 mg per kilogram total dose was infused intravenously over a period of five to 10 minutes until maximal vasodilation was obtained Maximal vasodilation was assumed to be present when the coronary sinus oxygen content measured at two minute intervals stabilized at high values with ongoing infusion At this moment another injection of differently labeled TM was given Immediately thereafter the heart was paced up to 200 beats per minute Blood oxygen contents were deter mined and again TM injected Thereafter, pacing was stopped and coronary sinus oxygen checked Under maintained maximal vasodilation the systemic pressure was lowered by Arfonad the ganglion blocking agent trimetaphan 0 025 to 0 05 mg per kilogram intravenously and the last TM injection was made Finally a coronary angiography was made using the Sones tech nique to ascertain complete closure of both ar teries by Ameroid constrictor Thereafter the an terior descending branch of the left coronary ar tery was opacified and the collaterals to the left circumflex and the right coronary artery demon strated

Results

Mortality rate and frequency of myocardial in farction The death rate following chronic occlu sion of the left circumflex coronary artery plus the right coronary artery was 35 per cent This is comparable with the data published in a previous study[9] At present we have a mortality rate of 35 2 per cent in a total population of 111 dogs with multiple chronic coronary occlusions When death occurred it happened in 75 per cent of the cases during the second and third week post operative This fits very well with the time of complete occlusion of the constrictor devices[3]

From the 22 surviving animals four developed myocardial infarction All four had a clearly visi

reserve is clearly diminished. The reduction in dilatory capacity is not only restricted to the collateralized areas but was also found in the apparently normal regions In the area perfused by a normal LAD coronary artery the endocardium has a quite normal dilatory reserve In the epicardium on the other hand the dilatory reserve is clearly compromised. The fact that this phenomenon is limited to the epicardium most probably has something to do with the anatomic situation in dogs it is well known that the collateral channels are localized exclusively epicardially[3] Four weeks after implantation of the ameroid constrictors that means about one week after complete occlusion of the coronary arteries the anastomotic channels are numerous small in diameter and connected at the arteriolar level to almost every sub branch of the patent artery[3] This means that the entire perfusion area of the occluded arteries is now connected with the epicardial vasculature of the unoccluded artery This may account for the transient reduction of dilatory reserve of the epicardial LAD region The pressure flow relation in the normal LAD epicardium needs further explanation Because of the additional collateral resistance the pressure flow curve for the collateral dependent area shows a higher critical closing pressure" (Fig 2) as was found in normal dogs Therefore the pressure flow relation for LAD epicardium must be a compound *curve which should* be divided into two compartments (Fig 2) The first compartment shows the pressure flow behavior of LAD epicardium at pressures between 15 and 30 mm Hg that means before collateral flow increases The next compartment starts at 30 mm. Hg and is much less steep because of the now opened collateral shunts This shunting mechanism will be discussed further Green Cosby and Radzow[14] studied pressure flow relationships in intact vascular beds After occlusion of the arterial supply to one of two adjacent capillary beds, metered inflow into the other artery is greater than the flow through its cognate bed, because of collateral flow to the occluded areas. This flow increase reflecting collateral flow is only possible when the artery itself is not a flow limiting factor In our situation the LAD *carries* the blood supply to the whole heart that means to three times its normal area Consequently under maximal dilation the LAD flow should increase 15 times in comparision with the normal control flow Under these conditions the LAD coronary artery can be flow limiting This is demonstrated in Fig 3 The sum of the LAD total flow plus the collateral flow (LC total) is plotted against perfusion pressure The curve obtained in this way is not significantly different ($p > 0.05$) from the pressure flow curve in normal dogs This means that the LAD coronary artery is flow limiting in the animals with chronic coronary occlusions four weeks after implantation Consequently the collaterals act as shunts and drain part of the blood away from the normal myocardium In the collateral dependent myocardium the endocardium has the lowest coronary reserve The epicardium is significantly better perfused but still receives less blood than the normal myocardium Consequently this severe reduction in dilatory reserve can lead to an imbalance in oxygen demand and supply when the heart is stressed This is probably the basic mechanism which underlies the absence of an increase in left ventricular dp/dt max during the infusion of dipyridamole The mechanism of collateral development and their structural changes were studied in detail by Schaper[3] He could *clearly* demonstrate that the pre existent anastomotic channels undergo an active growth process[15] This supports our findings that the dilatory reserve in the collateralized area is remarkably increased five months after implantation of the ameroid constrictors In this group of animals the collateral dependent endocardial flow reaches almost normal values In those parts of the myocardium that are perfused by the patent LAD a *higher* than normal dilatory reserve was found and the epicardial and endocardial muscle layers are almost equally well perfused The higher than normal dilatory reserve of the LAD dependent perfusion area can only be explained on *the basis of* growth of vessels in this supposedly normal vascular province Since the epicardial growth of collaterals leads to epicardial arterio arterial shunting from the LAD to the LC area the dilatory reserve of the epicardial LAD area is already diminished during periods of normal oxygen usage Any increase in the myocardial oxygen demand can now lead *not only* to tissue hypoxia in collateral dependent areas but also in the LAD area This in turn may lead to growth of supposedly normal vessels in a normal vascular province This hypothesis is strongly supported by the finding in clinical as

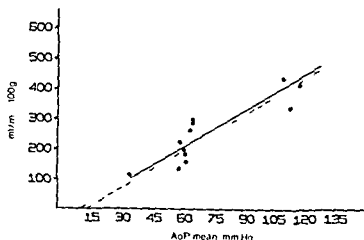


Fig 3 Relationship between the mean aortic pressure and the flow through the patent anterior descending branch of the left coronary artery in dogs with chronic coronary artery occlusion The sum of the LAD total flow plus the collateral flow is plotted against perfusion pressure The dotted line represents the pressure flow curve of the total LAD flow in normal dogs

rises the increase in flow is relatively small (Fig 2) At physiologic perfusion pressures (100 mm Hg) the LAD epicardial flow is only 170 ml per minute 100 Gm When the data obtained at pressure levels between 30 mm Hg and 125 mm Hg were extrapolated the intercept with the pressure axis becomes negative This lack in flow increase at higher pressure is also reflected in the ratio of endocardial to epicardial flow at normal pressures The mean value for this ratio was 2 05 (see Table I)

In the collateralized area (see Fig 2) the endocardial blood flow is significantly lower than the epicardial flow at every pressure level ($p < 0.05$ for sets of paired observations) At perfusion pressures in the physiologic range the endocardial flow reaches only 110 ml per minute 100 Gm (see Table I) The epicardial collateral flow in turn is significantly lower than the flow to the 'normal epicardium supplied by the LAD coronary artery ($p < 0.05$ for sets of paired observations) Due to the striking redistribution in flow during dilation oxygen consumption was not calculated Left ventricular dp/dt did not change significantly ($p > 0.05$) during maximal dilation

The distribution of myocardial flow was still nonhomogeneous five months after implantation of the ameroid constrictors (Group C) At normal pressures (AoPm = 100 mm Hg) higher than normal flows were reached in the LAD area (see Table I) The endocardial epicardial ratio was 1 11 and significantly different ($p < 0.05$) from the LAD endocardial epicardial ratio during maximal vasodilation in Group B At normal pressure levels, the flow to the collateral dependent area (LC area) was markedly increased in comparison with the collateral flow in Group B (Table I) However the endocardial layers still received less blood than the epicardium The endocardial epicardial ratio was 0 68

In Group C, no pressure flow curves were made Because of the reasons mentioned above oxygen consumption was not calculated Left ventricular dp/dt rose significantly ($p < 0.05$) during maximal vasodilation (Table I)

Regional flow distribution during maximal vasodilation plus pacing In six normal dogs the heart rate was increased to 200 beats per minute by ventricular pacing during maximal vasodilation The results are summarized in Table II The epicardial flow to the left ventricle did not change significantly during pacing while the endocardial flow decreased significantly ($p < 0.05$) The oxygen consumption rose significantly ($p < 0.05$) from 15 2 to 22 3 ml per minute 100 Gm Left ventricular dp/dt dropped significantly ($p < 0.05$) from 3 800 mm Hg per second to 3 050 mm Hg per second

In seven dogs four weeks after implantation of the constrictors the same procedure was followed. As described above the flow distribution was nonhomogeneous during maximal vasodilation During pacing this nonhomogenity became more outspoken the endocardial flow decreased significantly in both the LAD area and the collateral dependent area (LC) ($p < 0.05$) There was no change in the epicardial flows Left ventricular dp/dt max dropped significantly after ventricular pacing ($p < 0.05$) (see Table II)

Discussion

It is a well known fact that dogs with chronic coronary artery occlusions and good collateralization have a homogeneous myocardial flow distribution at rest [5,6] Also the finding that the endocardium is better perfused than the epicardium has been discussed widely in recent papers [11-13] The fall in oxygen consumption in the early phase of collateral development is difficult to explain Probably a resetting of the myocardial metabolism to a lower level plays a role

Of great importance for the conservation of myocardial structure and function is the dilatory capacity of the coronary bed In the early stages of collateral development the total coronary

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well as in experimental coronary occlusion of collateral localization within the perfusion area of a normal patent artery[1,3] rather than in the ischemic area

The last point to be discussed is the influence of pacing on the regional myocardial distribution Recently Buckberg and co workers[11] could demonstrate the relationship between diastolic pressure time index and the endocardial to epicardial flow ratio When the subendocardial vessels have lost their capacity to dilate flow to the endocardial layers depends upon diastolic blood pressure intramyocardial pressure coronary venous pressure and duration of diastole It was shown in dogs with normal coronary arteries that tachycardia induced by pacing during maximal vasodilation reduces subendocardial flow[16] This is confirmed by our findings However in normal dogs this situation does not lead to subendocardial ischemia since the oxygen demand is not increased to values which cannot be met by the supply In dogs with chronic coronary artery occlusions a reduction of subendocardial flow is much more likely to cause ischemia In the early stages after coronary artery occlusion the collateral dependent subendocardium is the most vulnerable part of the heart because of its severely compromised dilatory reserve As presented in Table II the subendocardial flow in the collateralized areas drops to 71 ml per minute 100 Gm $^{-1}$ during pacing plus maximal vasodilation We might expect, therefore that due to the pacing induced increase in oxygen demand and due to the diminished supply, the subendocardium in the collateral dependent myocardium becomes ischemic

Summary

We studied the influence of controlled changes in perfusion pressure and heart rate on the regional distribution of myocardial flow in normal dogs and in dogs with multiple chronic coronary artery occlusions but without infarctions

Local myocardial blood flow was determined with the tracer microsphere technique By stepwise altering of systemic blood pressure during maximal vasodilation classical pressure flow relations were obtained One week after complete chronic occlusion a functionally and anatomically well defined compartmentation of blood flow was found The dilatory reserve is clearly compromised not only in the collateral dependent myocardium but also in the apparently normal myocardium which delivers collateral flow An "arterio arterial shunting" mechanism is shown to exist Several months after coronary occlusion regional myocardial flow is still non homogeneous Although the coronary dilatory capacity of the collateralized myocardium is nearly normal, that of the normal myocardium is found to be higher than normal Vessel growth in both areas is discussed as being responsible for this phenomenon

Right ventricular pacing during maximal vasodilation produces a flow decrease to the endocardial muscle layers in normal dogs while the epicardial flow is unchanged One week after complete chronic coronary occlusion pacing during maximal vasodilation reduces the dilatory capacity in the collateralized areas to such an extent that the supplementary increase in myocardial oxygen demand will induce ischemia because of the compromised oxygen supply

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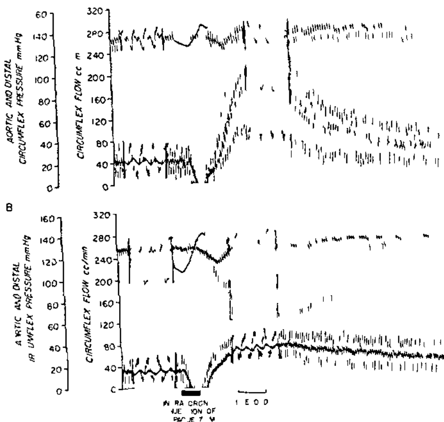


Fig 1 Representative pressure and flow tracings from a dog with no stenosis (*A*) and a moderately severe stenosis (*B*) while contrast was injected. This figure shows pressures and flow at rest followed by the pressure and flow responses after contrast injection indicated by the bar at the bottom of the figure Tracings are most easily distinguished in (*B*) where from top to bottom are aortic pressure distal circumflex pressure and phasic circumflex flow with mean circumflex flow superimposed. Mean pressure tracings have been removed for clarity In (*A*) the same lines are present but the pressures are superimposed at rest diverging only slightly in diastole during peak hyperemia In the absence of stenosis (*A*) flow increased markedly while only a slight aorta distal circumflex pressure gradient developed but with a severe stenosis (*B*) flow increased only slightly while the aorta distal circumflex pressure gradient increased markedly

was measured with a Zepeda square wave electromagnetic flowmeter operating at 400 Hz which was calibrated in vivo Both pressure and flow were recorded in the phasic and mean mode simultaneously A limb lead electrocardiogram was monitored.

The experimental procedure was as follows All dogs were heparinized intravenously (100 U per kilogram) Baseline resting flow was recorded, following which the artery was gently occluded with forceps for 10 seconds and the hyperemic flow response was recorded The distal circumflex catheter was then inserted Reactive hyperemia to 10 second occlusion was then repeated to verify that the distal circumflex catheter did not interfere with the flow response Coronary flow aortic and distal circumflex pressure were then recorded throughout the rest of the experiment In the five dogs in which a Sones catheter was used the pressure gradient between the aorta and distal circumflex artery at peak hyperemia was measured with the Sones catheter in and out of the coronary orifice to determine any obstruction to flow by the catheter Contrast media (sodium and meglumine diatrizoate Hypaque M 75 per cent) was then injected into the coronary artery through either the Sones or distal circumflex catheter The dose of contrast was constant in each dog averaging 3 4 c c (0 125 ± 0 01 c c per kilogram) sufficient for fluoroscopic opacification equivalent to that of clinical coronary angiography Before each injection coro

Mechanism of the effect of coronary artery stenosis on coronary flow in the dog

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Clinical studies have shown that the diseased coronary arterial system supplies normal coronary flow at rest however there is conflicting evidence as to whether this flow increases appropriately in response to hyperemic stimuli [1-16] Although the study of this situation is difficult in man because of the inability to directly measure vessel flow dog studies in which coronary flow was directly measured have shown that progressive stenosis initially limits the maximum hyperemic response and only after the stenosis has progressed to the severity that this response is almost abolished does it decrease resting flow [17-19] While this effect of stenosis on flow is known the hemodynamic mechanism of this effect is unclear Accordingly the purpose of this study is to define this mechanism To accomplish this angiographic contrast media an agent known to maximally but transiently vasodilate the coronary bed [19] was injected into the variably stenotic dog coronary artery while the hemodynamic relationships of the stenosis and distal bed were studied separately and interdependently

Methods

Ten consecutive, 22 to 40 kilogram Black Labrador or German Shepherd dogs were studied Each was given 45 mg of morphine sulfate intramuscularly one hour prior to the procedure followed by intravenous sodium pentobarbital (20 mg per kilogram) initially and as needed for anesthesia Respiration was maintained with a Harvard ventilatory pump through a cuffed endotrachael tube and blood Po_2 kept between 90 and 150 using supplemental oxygen as necessary

The chest was entered through a left thoracotomy and the circumflex coronary artery was isolated An electromagnetic flow probe (Zepeda) with a lumen slightly smaller than the artery was placed just distal to the bifurcation from the left anterior descending artery A variable constrictor was placed 0 5 cm distal to the flow probe This constrictor consisted of a 3 mm wide umbilical tape which passed around the artery and through an interposed length of stiff tubing to a micrometer such that the artery could be constricted in precise increments Approximately 1 5 cm distal to the constrictor and just proximal to the first major circumflex bifurcation a 1 mm outside diameter teflon end hole catheter (Bardic 1968 T) was inserted pointing upstream hereafter this catheter is called the distal circumflex catheter Any small branches between the flow probe and distal circumflex catheter were ligated A No 8 French side hole catheter was introduced through the right carotid artery and the end placed just above the aortic valve In five dogs a Sones coronary arteriography catheter was introduced through the left carotid artery

All measurements were recorded on an Electronics for Medicine DR 12 recorder at paper speeds varying from 25 to 100 mm per second Pressures were obtained through the aortic and distal circumflex catheters with a Kulite PSL 125 6 and a Statham P 23 Db pressure transducer which were matched before during and after the procedure Circumflex coronary flow

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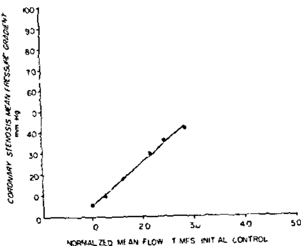


Fig 4 Representative relationship between flow and pressure gradient for one moderately severe stenosis Points were taken at maximum hyperemia at rest and at intermediate flow levels

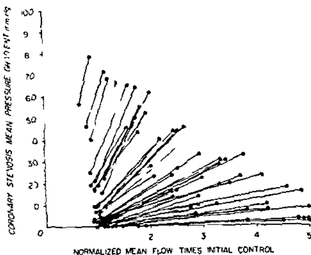


Fig 5 Regression lines relating pressure gradient to flow for 44 stenoses. Each line was drawn from 5 to 10 points as shown in Fig 4 The median correlation coefficient was 0 99 The degree of stenosis ranged from minimal (flat lines) to severe (steep lines)

response decreasing only 13 ± 6 per cent from the beginning to the end of the experiment

Distal bed hemodynamics The distal bed was defined as that part of the coronary vascular system distal to the distal circumflex catheter while the proximal coronary artery was defined as the artery proximal to the catheter By measuring distal bed perfusion pressure through the distal circumflex catheter the relationship of flow to distal bed pressure could be studied as this pressure was varied by changing the degree of stenosis As shown in Fig 2 resting coronary flow stayed at initial control level despite decreasing distal bed pressure until this pressure was dropped to approximately 60 mm Hg Below this pressure flow was linearly related to distal bed pressure a relationship which could be expressed as Δ distal bed pressure/Δ normalized flow and termed distal bed resistance Thus in the resting state when distal bed pressure was reduced below 60 mm. Hg distal bed resistance decreased to a minimal fixed value of 40 mm Hg/normalized flow but when pressure was increased above 60 mm Hg resistance was autoregulated such that resting flow was kept constant at initial control level Since at the minimal fixed resistance the regression line correlating pressure and flow crossed the pressure axis at 16 mm. Hg a point termed the critical closing pressure the absolute relationship of pressure to flow was given by

$$DBP = (DBR \times F) + CCP \qquad (1)$$

where DBP = distal bed pressure DBR = distal bed resistance (Δ distal bed pressure/Δ normalized flow) F = normalized flow and CCP = critical closing pressure of distal bed.

The relationship of flow to distal bed pressure at peak hyperemia was examined in similar fashion to that at rest only the points were taken at the time of maximum response to contrast one point for each stenosis As shown in Fig 3 the relationship was linear indicating that at maximum vasodilation distal bed resistance was constant regardless of the severity of stenosis This value was 20 mm Hg/normalized flow a value less than the minimum resistance resulting from decreased pressure alone However the regression line representing this relationship also crossed the pressure axis at the critical closing pressure of 16 mm Hg such that Equation 1 could also be used to describe this relationship using the value of 20 mm. Hg/normalized flow for distal bed resistance

Coronary stenosis hemodynamics The isolated hemodynamics of the coronary stenosis were studied by plotting 5 to 10 points comparing the pressure gradient across the stenosis to flow through the stenosis as flow was transiently varied by contrast injection An example of this relationship for one stenosis is shown in Fig 4

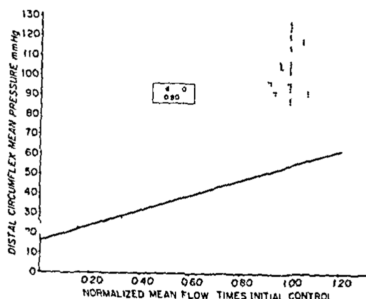


Fig 2 Relationship of mean coronary flow to mean distal bed pressure at rest Distal bed pressure was varied by changes in the stenosis The regression line was determined from all points below 60 mm Hg Its slope represents the minimum distal bed resistance at rest

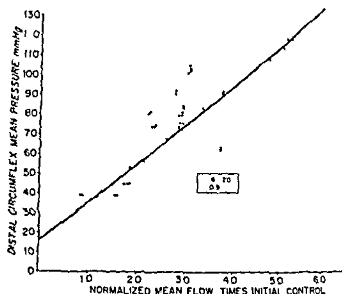


Fig 3 Relationship of mean coronary flow to mean distal bed pressure at the point of maximum hyperemia after contrast Distal bed pressure was varied by changes in the stenosis The slope of the regression line represents the distal bed resistance at maximum hyperemia

nary flow aortic and distal circumflex pressures were allowed to stabilize Contrast medium was then injected while these variables were continuously recorded After pressure and flow returned to pre injection levels, the constrictor was tightened and contrast injection repeated In 14 to 22 such steps the constrictor was tightened to complete occlusion After total occlusion the constrictor was removed and flow allowed to stabilize The flow response to 10 second occlusion was then measured to compare with the pre experiment response After removal of the flow probe 10 second occlusion was again performed to determine the effect of the flow probe on the pressure gradient at peak hyperemia

All pressures and flows were analyzed as their mean value Flows were normalized to each dog s resting flow at the beginning of the experiment (hereafter termed initial control flow) The data was analyzed with a Digital PDP 8 computer Values were expressed as the mean ± standard error of the mean Differences were tested for significance by the Student s t test Regression lines were drawn by the least squares fitting test [20] The regression line in Fig 3 was fitted after fixing the pressure axis intercept [21]

Results

Typical records of aortic pressure distal circumflex pressure and coronary flow recorded during contrast injection are shown in Fig 1 The upper tracing, (*A*) was recorded with no stenosis present and shows a slight gradient develop between the aorta and distal circumflex during hyperemia while flow increases markedly The lower tracing (*B*), was recorded with a moderately severe stenosis and in contrast to the unstenosed artery shows the gradient increase markedly while flow increases relatively little

Initial control resting flow averaged 48 ± 15 c c per minute and after contrast injection increased 4 2 ± 0 4 times resting a response 6 ± 6 per cent greater than that following a 10 second occlusion The heart rate was 151 ± 2 beats per minute and the mean aortic pressure was 110 ± 1 mm Hg Systemic changes after contrast injection were minimal averaging a decrease of 2 ± 0 4 beats per minute in the heart rate and 5 ± 0 5 mm Hg in the mean aortic pressure

Verification of method The flow probe caused a 1 4 ± 0 5 mm Hg gradient at peak hyperemia and was disregarded in later calculations The Sones catheter in the coronary orifice caused no significant gradient at peak hyperemia (0 5 ± 0 6 mm Hg) Insertion of the catheter in the distal circumflex caused a 6 ± 5 per cent decline in peak flow after 10 second occlusion a statistically insignificant amount The stability of the preparation was documented by the peak flow

trates the capacity of the coronary arterial system to increase flow from the resting to the maximally hyperemic state and how this ratio decreased as coronary stenosis increased In Equation 5 low fixed levels of stenosis resistance were dominated by the higher values of distal bed resistance allowing changes in distal bed resistance to be reflected by relatively large changes in flow In contrast high fixed levels of stenosis resistance dominated the equation such that changes in distal bed resistance were reflected by relatively small changes in flow An additional factor which affected the change in flow from resting to hyperemia was that as stenosis resistance increased, resting distal bed resistance decreased to keep resting flow at control level This decreased the amount of change in distal bed resistance when the resistance was changed from its resting to hyperemic state thereby causing less change in flow

Discussion

Angiographic contrast media was used as the hyperemic stimulus in this study because of its maximum vasodilatory ability and rapid reversibility of effect Contrast has been shown to cause maximum vasodilation since the peak flow after its injection is essentially the same as that following 10 second occlusion of the vessel [19] an observation confirmed in this study Previous studies have shown that the peak flow rate after 10 second occlusion is the same as that after much longer occlusion and exceeds the flow rate with heavy exercise or excitement and furthermore is unaffected by vasodilator or beta blocking agents, cardiac denervation or simultaneous occlusion of the other coronary arteries [18 22 24] Although the dose of injected contrast was not precisely controlled due to the varying amount of myocardium supplied and some loss into the aorta the similarity of flow responses suggested that the doses administered were on a plateau of the hypothetical dose response curve Clinical studies using isotopic methods to measure coronary flow after contrast injection have shown much lower flow responses to contrast [26] however the methodology necessitated flow measurement much later after injection at a time which our study would indicate was well after the peak response

The regression lines relating flow to distal bed pressure crossed the pressure axis at approximately 16 mm Hg both in the resting state and after contrast This pressure where flow ceases has long been recognized in skeletal muscle and termed critical closing pressure [27] More recently Mosher and associates observed the same phenomenon in the heart using a coronary perfusion technique [28]

With a given stenosis the pressure gradient across the stenosis varied linearly with the flow through it, a finding predicted by Poiseulles equation [27] However an unexpected finding was that the regression line relating pressure gradient and flow did not intercept the flow axis at zero flow but instead, intercepted it at a significantly positive flow Although we are unable to explain this finding support for its validity is gained from similar pressure gradient flow curves in a postmortem study by Schultz Hokanson and Strandness[29] in which diseased femoral arteries were perfused. In all cases of significant stenosis this flow axis intercept of the regression line was beyond the extent of collected data therefore we do not mean to imply that the pressure gradient necessarily decreases to zero before flow ceases The position of the intercept is only used to identify the position of a regression line with a given slope

Decreased distal bed pressure has been shown to be an important cause of subendocardial ischemia [30-33] Since distal bed pressure is inversely related to the stenosis pressure gradient which is in turn determined by the flow through the stenosis Fig 5 illustrates the critical effect that seemingly minor changes in flow through a severe stenosis have on the distal bed pressure Through this mechanism factors which increase coronary flow may lead to a steal phenomenon i e increased subepicardial flow causes increased flow through the stenosis increasing the pressure gradient and decreasing distal bed pressure thereby resulting in decreased subendocardial flow Conversely factors which tend to decrease coronary flow may have an opposite effect, tending to improve subendocardial perfusion

Summary

The hemodynamic mechanism of the effect of coronary artery stenosis on coronary flow was studied in the circumflex artery of 10 open chest dogs by simultaneously measuring coronary flow

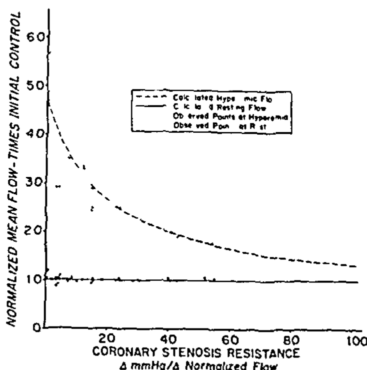


Fig 6 Effect of coronary stenosis resistance on resting flow (solid line solid dots) and maximally hyperemic flow (dashed line open circles) The lines represent the calculated values from Equation 5 while the points represent the observed values

Forty four stenoses of varying severity were studied in this manner and a composite of all their regression lines is illustrated by Fig 5 All stenoses showed a highly linear relationship be tween pressure gradient and flow with a median correlation coefficient of 0 99 The slope of the re gression line Δ pressure gradient/Δ normalized flow, indicated the physiologic severity of the stenosis and was termed coronary stenosis resist ance

An unexpected, but highly significant finding was that the regression lines relating pressure gradient to flow all intercepted the flow axis (zero pressure gradient) at a significantly positive flow Although this intercept tended to be higher with low stenosis resistances and lower with high resistances, it averaged 0 65 ± 0 03 times initial control flow for all stenoses in which a resting pressure gradient was present. Using this inter cept and coronary stenosis resistance the rela tionship of pressure gradient to flow could be ex pressed as

$$PG = CSR \times (F\ FAI) \qquad (2)$$

where PG = mean pressure gradient across stenosis CSR = coronary stenosis resistance (Δ pressure gradient/Δ normalized flow) and FAI = flow axis intercept of the stenosis pressure gradient flow regression line

Relationship of flow to stenosis resistance The theoretical relationship of coronary flow to coronary stenosis resistance was derived from the pressure flow relationships of the distal bed coronary stenosis. By definition

$$AoP = DBP + PG \qquad (3)$$

where AoP = aortic pressure Substituting For mulas 1 and 2 into 3, and rearranging

$$F = \frac{AoP - CCP + (FAI \times CSR)}{DBR + CSR} \qquad (4)$$

Substituting the relatively constant aortic pressure critical closing pressure and flow axis intercept gave

$$F = \frac{0\ 65\ CSR + 94}{DBR + CSR} \qquad (5)$$

In the resting state flow was dependent on both stenosis and distal bed resistance at low and moderate values of stenosis resistance since dis tal bed resistance was autoregulated to keep flow at its control resting value However as stenosis resistance was increased distal bed resistance decreased until it reached its minimum resting value of 40 mm Hg/normalized flow As stenosis resistance was increased beyond this point flow was directly dependent on stenosis resistance and fell below its control resting value The solid line in Fig 6 illustrates that calculated resting flow remained at initial control level as stenosis resistance increased to the relatively severe value of 100, while the solid points indicate the observed values Few data points are given at the highest resistance values because flow did not vary sufficiently to calculate a stenosis resist ance

In the postcontrast maximally hyperemic state flow was dependent only on stenosis resis tance since distal bed resistance was fixed Therefore any change in stenosis resistance resulted in a change in maximum flow The dashed line in Fig 6 indicates this predicted rela tionship from Formula 5 while the open circles indicate the observed values

Comparison of the two curves in Fig 6 illus

25 Raff W K Kosche F and Lochner W Extravascular coronary resistance and its relation to microcirculation influence of heart rate end diastolic pressure and maximal rate of rise of intraventricular pressure Am J Cardiol 29 598 197?

26 Kloster F E Friesen W G Green G S and Judkins M P Effects of coronary arteriography on myocardial blood flow Circulation 46 438 1972

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aortic pressure, and coronary artery pressure distal to an adjustable constrictor while the distal coronary bed was intermittently maximally vasodilated by intracoronary injections of angiographic contrast media (Hypaque M, 75 per cent) For each stenosis the pressure gradient across the stenosis varied directly with the flow through the stenosis (r = 0 99), the slope of the regression indicating the severity of the stenosis. An important observation was that this regression line did not intercept the flow axis at zero flow but at a positive flow, meaning that for a given regression line slope the pressure gradient was much less than expected At rest, distal bed resistance decreased as progressive stenosis lowered the distal bed pressure maintaining flow at control level until the distal bed pressure dropped below 60 mm Hg However, at maximum hyperemia, distal bed resistance was at a fixed minimum value such that flow was directly proportional to distal bed pressure Hence, progressive stenosis decreased the ratio of hyperemic to resting flow by (1) causing the vasodilatory reserve to be used to maintain resting flow decreasing that available for hyperemia and (2) dropping the distal bed pressure relatively more for smaller increases in flow This study provides a hemodynamic explanation for the known fact that progressive stenosis initially limits the maximum hyperemic flow and only after this flow is decreased almost to resting level does resting flow fall

The technical assistance of Miss Cynthia Calvert is gratefully acknowledged

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Effect of stimulation site on ventricular threshold in dogs with heart block

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While most studies have shown that threshold energy requirements are less with endocardial than with intramyocardial ventricular stimulation [2 8 11 12 14] a few reports have concluded that intramyocardial stimulation is electrically superior [5 7 9] Interpretation of this conflicting data is difficult due to the use of indirect measurement techniques[7] electrodes of unlike configuration material and/or cross sectional area at the sites being compared[2 12 14] and lack of metabolic control during threshold determinations [22]

We were therefore led to reinvestigate the effect of electrode location on ventricular threshold energy requirements in dogs with complete heart block Identical electrodes were used at all stimulation sites Current and voltage parameters including polarization losses were determined directly using an oscilloscope and current probe

Methods

Twenty mongrel dogs weighing 15 to 20 kilograms were placed on thermostatically regulated warming trays and anesthetized with sodium pentobarbital (30 mg per kilogram) An endotracheal tube was inserted and connected to a volume cycled respirator Appropriate respirator and oxygen flow adjustments and $NaHCO_3$ administrations were made to maintain a Po_2 of 100 mm Hg ± 20 Pco_2 of 40 ± 5 mm Hg pH of

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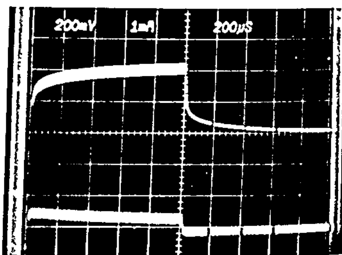


Fig 1 Polaroid photograph of left ventricular apical intramyocardial stimulation showing little polarization The upper trace is voltage and lower trace is current (milliamperes) Calibrations of the oscilloscope (units per division) are illuminated directly on the screen so that errors in determination are eliminated

7 4 ± 0 1 and base excess of less than ± 2 Small surface area (1 2 mm in diameter), Elgiloy ball tip electrodes were placed intramyocardially on the left and right ventricular apices and transvenously into the right ventricular apex Complete heart block was induced by injecting formalin into the bundle of His by a closed heart technique [19] Thirty minutes were allowed for stabilization during which time the heart was paced at 100 beats per minute Myocardial cathodal stimulation was used throughout the study The anode was a 10 cm ^{2} subcutaneous stainless steel plate After determination of physiologic pH blood gas electrolyte and body temperature strength duration curves were derived for each stimulation site using a custom designed low rise time low impedance balanced square wave generator Threshold currents and voltages were measured directly using a Tektronix 7504 oscil

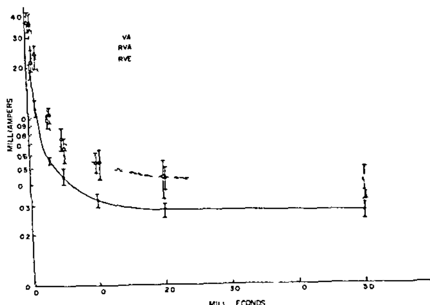


Fig 2 Strength duration curves for the threshold current (mean ± S E) requirements of the ball tip electrode at three ventricular sites LVA left ventricular apex—intramyocardial RVA right ventricular apex—intramyocardial and RVE right ventricular apex—endocardial

loscope and P6042 current probe at seven stimulus durations from 0 05 to 5 0 msec The order of lead stimulation was randomized and at the conclusion of each trial all leads were re evaluated to confirm stability of the experimental model Threshold was defined as the minimum current and voltage required to achieve a sustained 1 1 coupling of stimulus and ventricular contraction Stimulus parameters were measured directly and photographically recorded with a system that precludes errors in measurement or in interpretation by providing digital sensitivity readings for voltage current and pulse width on the oscilloscopic screen (Fig 1) Energy calculations were made by integrating the area under the entire wave form and included polarization losses The significance of the threshold differences found between the various leads studied were determined using the paired t test

Results

The left ventricular apical intramyocardial lead always required less current at threshold than either the right ventricular apical intramyocardial lead or the right ventricular endocardial lead These differences were significant at stimulus durations of 0 05 msec ($p<0.01$) 0 1 msec ($p<0.01$) 0 3 msec ($p<0.01$) 0 5 msec ($p<0.025$) and 1 0 msec ($p<0.025$) There were no differences in current requirements between the right ventricular apical intramyocardial and right ventricular endocardial sites at any stimulus duration Comparative current strength duration curves for the three myocardial sites studied are shown in Fig 2

Threshold voltage requirements were lower for the left ventricular intramyocardial site than for the right ventricular intramyocardial site at all stimulus durations Threshold voltage requirements were lower for the left ventricular intramyocardial site than for the right ventricular endocardial site except at the 2 0 and 5 0 msec durations These differences were significant at stimulus durations of 0 05 msec ($p<0.01$) 0 1 msec ($p<0.01$) 0 3 msec ($p<0.01$) and 0 5 msec ($p<0.025$) At 1 0 msec left ventricular intramyocardial stimulation required less threshold voltage than right ventricular intramyocardial stimulation ($p<0.05$) but was not significantly different than right ventricular endocardial stimulation The two right ventricular sites were significantly different only at 5 0 msec ($p<0.05$) when the endocardial site required less threshold voltage Threshold voltage for the left ventricular apical intramyocardial and right ventricular apical intramyocardial electrodes reached rheobase at 1 0 msec and 2 0 msec respectively

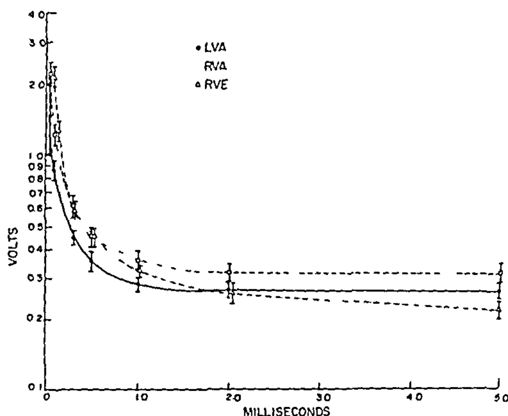


Fig 3 Strength duration curves for the threshold voltage (mean ± S E.) requirements of the ball tip electrode at three ventricular sites Abbreviations same as in Fig 1

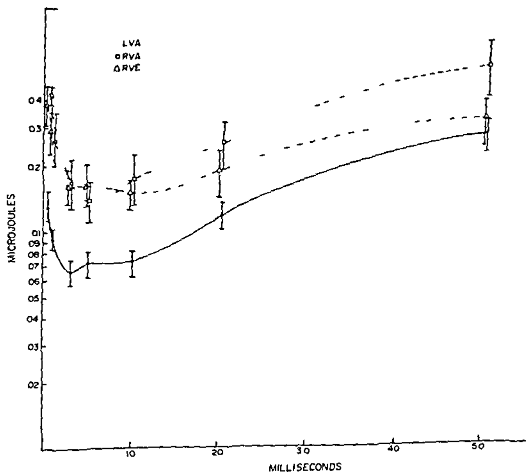


Fig 4 Strength duration curves for the threshold energy (mean ± S E) requirements of the ball tip electrode at three ventricular sites The different area of optimal pulse width (lowest energy requirement) for each lead can be easily seen Abbreviations same as in Fig 1

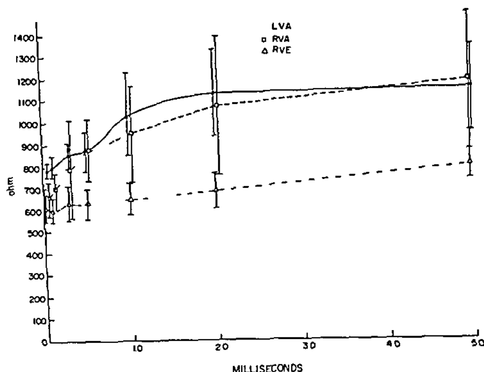


Fig 5 Threshold impedance duration curves (mean ± S E.) for the ball tip electrode at three ventricular sites Impedance was found to be inversely related to threshold requirements Abbreviations same as in Fig 1

while the right ventricular endocardial electrode achieved rheobase only at longer stimulus durations Comparative voltage duration curves are shown in Fig 3

Mean threshold energy requirements with the left ventricular intramyocardial electrode were significantly lower than with the right ventricular intramyocardial electrode at all stimulus durations and were lower than with the right ventricular endocardial electrode at all durations except 5 0 msec (all p<0 01) No significant differences in energy requirements were noted when the right ventricular sites were compared with each other except at 5 0 msec when the endocardial site required significantly less energy (p<0 05) Comparative threshold energy duration curves for the three sites studied are illustrated in Fig 4 Optimal pulse width was defined as the stimulus duration at which the least energy was required to achieve a continuous 1 1 coupling of stimulus and ventricular contraction For left ventricular intramyocardial stimulation this was at 0 3 msec (0 07 ± 0 09 microjoules) for right ventricular intramyocardial stimulation at 0 5 msec (0 14 ± 0 03 microjoules) and for right ventricular endocardial stimulation at 1 0 msec (0 15 ± 0 02 microjoules) When compared with left ventricular intramyocardial stimulation at pulse durations of 0 05 to 2 0 msec. inclusive right ventricular intramyocardial and endocardial stimulation significantly increased energy losses due to polarization (p<0 05) Polarization losses were identical for the two right ventricular sites

Threshold impedance was calculated (impedance in ohms = voltage divided by current in amperes) for all sites and stimulus durations (Fig 5) No significant difference in impedance was found when the two intramyocardial sites were compared The impedance of the right ventricular endocardial site however was significantly lower than that of the left ventricular intramyocardial site at all stimulus durations (p<0 025)

Mean chronaxy was 0 26 ± 0 03 msec with left ventricular intramyocardial stimulation 0 31 ± 0 03 msec with right ventricular intramyocardial stimulation and 0 49 ± 0 06 msec with right ventricular endocardial stimulation The chronaxy for right ventricular endocardial stimulation was significantly longer than for left ventricular intramyocardial stimulation (p<0 02) and right ventricular intramyocardial

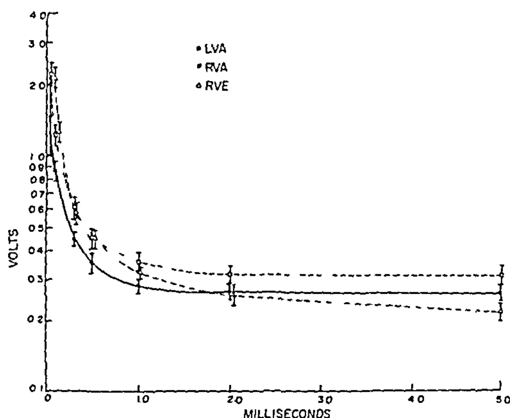


Fig 3 Strength duration curves for the threshold voltage (mean ± S E) requirements of the ball tip electrode at three ventricular sites Abbreviations same as in Fig 1

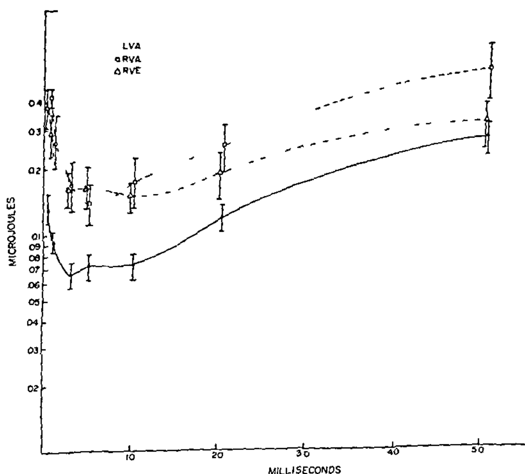


Fig 4 Strength duration curves for the threshold energy (mean ± S E) requirements of the ball tip electrode at three ventricular sites The different area of optimal pulse width (lowest energy requirement) for each lead can be easily seen Abbreviations same as in Fig 1

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stimulation (p<0 05) There was no significant difference in chronaxy when the intramyocardial sites were compared

Discussion

Many variables affect ventricular stimulation threshold energy requirements Primary determinants include electrode material,[5,16,24] electrode cross sectional area[2,4,21] electrode configuration,[18,10] stimulus polarity,[15,23] stimulus wave form,[24] stimulus duration,[3] and physiologic factors such as drug administration[1,6] exercise,[1,18] electrolyte concentrations in the extracellular fluid[18] and acid base balance[22] Secondary determinants of threshold energy include current density electrode polarization electrochemical reactivity at the electrode electrolyte interface[4,6,16,17,20] and local and general impedance[13,20] In previous studies of the effect of stimulation site on threshold energy requirements one or more of these electrode variables were not controlled frequently biasing the results in favor of the endocardial site When identical electrode systems were used as in the present study the voltage required for threshold stimulation with the right ventricular endocardial lead fell progressively with increasing pulse duration, however rhe obase was reached at 1 0 and 2 0 msec with the left and right ventricular intramyocardial leads respectively Current consumption roughly paralleled the voltage requirements Energy consumption was highest at the shorter and longer stimulus durations with the lowest consumption occurring between 0 3 and 1 0 msec depending upon stimulation site The chronaxy of each stimulation site was somewhat shorter than the stimulus duration at which least energy was consumed The impedance was lowest with endocardial stimulation and thus impedance appears to be inversely related to energy consumption and chronaxy

The highest threshold values obtained were with the right ventricular endocardial lead The endocardium like the epicardium may act to somewhat insulate the myocardial conduction system from the electrical stimulus[10,14] In addition, the tip of the endocardial electrode is partially immersed in a conducting fluid (blood) which may dissipate some of the stimulus energy

The lowest threshold values were obtained with the left ventricular intramyocardial electrode Accurate placement of intramyocardial electrodes is accomplished with ease and the incidence of electrode dislocation is minimal. The relatively thick left ventricular wall has a high density of Purkinje fibers and perforation through to the endocardium or cavity is unlikely

Summary

Ventricular pacing thresholds were measured in barbiturate anesthetized dogs with complete heart block using an oscilloscope and current probe All electrode and physiologic variables were carefully controlled in order to compare the effects of stimulus duration and site of ventricular threshold energy requirements Left ventricular intramyocardial stimulation at all stimulus durations under 5 msec required less current and energy and at all stimulus durations under 2 msec less voltage than either right ventricular endocardial or right ventricular intramyocardial stimulation Chronaxy and polarization losses were lowest and impedance highest with left ventricular intramyocardial stimulation The two right ventricular sites were almost equivalent electrically Earlier studies which reported lower thresholds with endocardial stimulation than with intramyocardial stimulation were biased in favor of the endocardial site by lack of control of electrode variables including material configuration cross sectional area and epicardial versus intramyocardial location

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Electrophysiology of atrial pacing in patients with short PR interval, normal QRS complex

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Four recent studies have investigated the syndrome of short PR interval normal QRS complex [1-3, 5] These investigations stem from the study by Lown, Ganong and Levine[4] in 1952 describing 200 patients with a short PR interval of 0 12 second or less and a normal QRS complex It was noted at that time that 11 per cent of these patients had supraventricular tachycardia The mechanisms of both the short PR interval and the supraventricular tachycardia remain obscure Two recent reports by Castellanos and co workers[3] and Mandel Danzig and Hayakawa [2] utilizing His bundle recordings attempted to determine the mechanism involved in this syndrome The Castellanos group studied three patients and concluded the short PR interval was due to an abbreviated A V node conduction time His Purkinje conduction was normal Mandel s group studied three patients and determined that the His Purkinje time was short and the cause of the short PR interval The largest study by Caracta and co workers[1] studies 18 patients with 42 per cent incidence of subjective tachycardia and documented in 27 per cent They found as did Castellanos and co workers, that the shortened PR interval was due to an abbreviated A V nodal conduction time and not H V conduction time Another study by Bissett and co workers,[6] utilizing the same technique, also noted that the shortened conduction time is due to an abbreviated A V nodal conduction This report further examines the type of response noted with atrial pacing on the A V conduction system in patients with a short PR interval and normal QRS

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Materials and methods

Ten patients were studied three males and seven females, aged 16 to 55 with an average age of 31 All patients had PR intervals of 0 12 second or less and a QRS duration of 0 09 second or less as determined by 12 lead electrocardiogram An additional primary indication for study was a history of tachycardia or significant palpitations The presence of heart disease was determined by clinical history, physical examination chest x ray, and cardiac catheterization if indicated a screening laboratory test including T 3 and T 4 All ten patients gave a history of palpitations of rapid nature, usually bothersome and disabling in four patients Of these four patients, three had documented episodes of tachycardia None of the patients were on drugs at the time of the study The purpose and nature of the study were explained to all the patients and consent was obtained Cardiac catheterization was performed with the use of local lidocaine anesthesia All of the patients were in a supine and postabsorptive sedated state using Demerol and Phenergan A hexa polar catheter was advanced by way of the right femoral vein to the right atrium into the area of the tricuspid valve A second catheter was advanced along the right basilic vein to the junction of the right atria and superior vena cava This electrode was used to stimulate the right atrium while the second catheter was used to record His bundle electrograms Recordings of two standard electrocardiographic leads (I and III) were also obtained Electrocardiograms with time lines at 50 and 100 msec were displayed on a multichannel oscilloscope (Electronics for Medicine) recorder Electrograms were filtered at a frequency setting of 40 to 500 Hz In all the patients atrial pacings at various rates were performed using a battery powered Medtronics No 5837 that delivered impulses at 2 msec duration

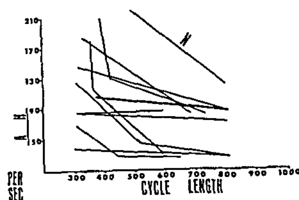


Fig 1 Composite of all ten patients showing the variable response to atrial pacing compared with (N) normal

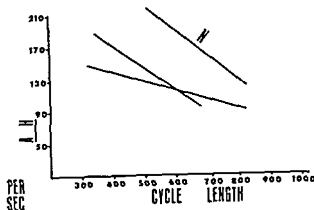


Fig 3 Response of two patients to atrial pacing Type II (see text)

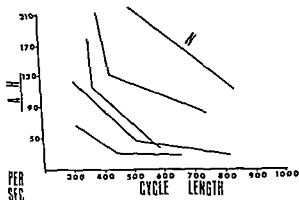


Fig 2 Response of four patients to atrial pacing demonstrating Wenckebach cycling Types Ia and Ib (see text)

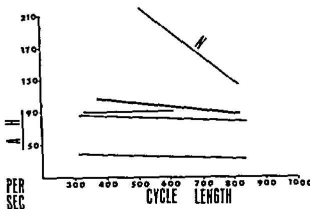


Fig 4 Response of four patients to atrial pacing with no increase in AH interval Type III (see text)

at approximately twice diastolic threshold level Care was taken to ground all electrical equipment [6,7]

Results

The normal range for A H interval is 70 to 140 msec and H V is 30 to 55 msec in patients with PR intervals greater than 0 12 second In seven of the ten patients, the short PR interval was due to an A H that was closer to lower limits of normal In five of the patients, it was lower than normal two at the lowest limit of normal and three in the normal range In none of the patients was the shortened PR interval due to an H V interval that was below 30 msec

Table I lists the clinical data of the ten patients

The consistent finding among the group of patients was that the PR interval was short in all ten patients Five of the ten patients had documented episodes of tachycardia with the exception of Patient No 3 in whom paroxysmal atrial tachycardia was induced at catheterization and spontaneously (Figs 5 and 6) The other three patients (Nos 2 7 and 9) had spontaneous episodes of tachycardia documented outside of the cardiac catheterization laboratory There is no consistency between the A H interval and the H V intervals to suggest that as an indicator of A H responsiveness The types of arrhythmia are noted in Table I

Response to atrial pacing Fig 1 is a composite of the ten cases and a response to atrial pacing at various cycle lengths N stands for the curve of normals There is a variety of A V nodal responses Fig 2 depicts a Type I response This group of patients all demonstrate Wenckebach periods with short A H intervals and varying degrees of A V nodal response If a straight line is drawn from the end of the Wenckebach period to the resting stage it will generally parallel normal but is of course of shorter duration Fig 3

Table I Clinical data on ten patients (in milliseconds)

	Sinus cycle length	AH	HV	DX	HX of SVT	APC VPC	Atrial pacing AH	Arrhythmia
1	800	40	35	PAT	Yes	No	NC	
2	800	85	35	PAT	Yes	No	Increase AH	Sinus tachycardia
3	670	35	30	PAT	Yes	No	Increase AH	PAT induced
4	650	90	28	PAT	Yes	No	NC	
5	800	80	35	PAT	Yes	No	Increase AH	
6	800	55	45	PAT	Yes	No	Increase AH	
7	600	50	55	PAT	Yes	No	Increase AH	Junctional tachycardia
8	1050	55	55	PAT	Yes	No	Increase AH	
9	770	70	50	Atrial FIB	Yes	Atrial FIB	NC	Atrial FIB
10	830	70	40	PAT	Yes	No	NC	PAT induced

Dx diagnosis Hx history SVT supraventricular tachycardia APC atrial premature contractions VPC ventricular premature contractions and NC no change

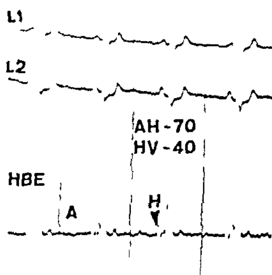


Fig 5 Paper speed 25 mm per second Patient No 10 with Type III response demonstrating short AH interval at rest AH 70 msec HV 40 msec

depicts two patients with Type II response who prolong their A H interval without abrupt onset of Wenckebach periods and again parallel the normal

Fig 4 demonstrates four patients Type III response, none of whom showed significant increases in the A H interval although paced at rates of up to 200 beats per minute They conducted 1 1 The H V time remained constant (Figs 5 and 7)

Discussion

In Lown and co workers[4] original discussion of the entity the majority of patients were middle aged women without evidence of heart disease Eleven per cent of these patients had evidence of supraventricular tachycardia To enter into this study the patient had to have a history of tachycardia As noted 5 out of the 10 patients (or 50 per cent) had documentation of tachyarrhythmia None of the patients had evidence of significant heart disease Two of the patients had mid systolic click and late systolic murmur syndrome Both of these patients had normal echocardiograms The above findings concur with those of Castellanos Caracta and Bissett who also found shortening A H intervals as the cause of the short PR Interval No patient was found with an abbreviated H V interval

The patients depicted in Fig 2 can be further divided into Type Ia and Ib Type Ia has a more gradual A H prolongation and Wenckebach block which develops at an earlier period than those with more rapidly increasing A H intervals This suggests that at some critical point conduction may have started through the normal pathway and the bypass tract was refractory Type Ib patients increased their A H intervals more rapidly at lower pacing rates but developed Wenckebach block later This sudden increase in A H interval resulted in dropped beats suggesting that the threshold for conduction was reached with more rapid rates and with prolonged A H conduction

Patients with Type II response (Fig 3) again represent partial normal and partial bypass conduction The shortened A H interval represented the bypass part of the conduction and the normal slope and delay represented the A V nodal conduction

Type III responses (Fig 4) are the most in

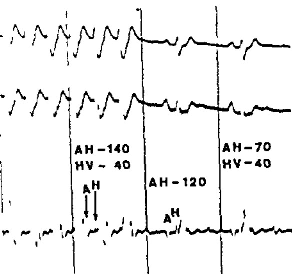


Fig 6 Paper speed, 25 mm per second. Patient No 10 during paroxysmal atrial tachycardia at 180 beats per minute in cluded at catheterization with AH 140 msec Posttachycar dial shortening of AH to 70 The first normal sinus beat has a prolonged AH of 120 msec suggesting fatigue of the A V node and probable involvement in the re entry circuit

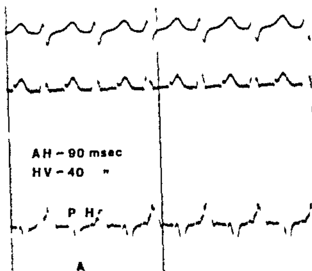


Fig 7 Paper speed 50 mm. per second. Patient No. 10 Atrial pacing at 178 beats per minute with 1 1 ventricular response and minimal AH prolongation P is the atrial pacemaker ar tifact

teresting patients and probably represent com plete absence of any A V nodal conduction This may be due to the absence of the A V node or use of altered bypass tract conduction at the expense of A V nodal conduction They clearly do not in crease their A H intervals which is a normal function of the A V node Two of Caracta s 18 pa tients and four in the present group did not in crease their A H interval during atrial pacing and this is thought to be consistent with complete bypass of the A V node as suggested by James involving the posterior internodal tract This unusual response is in marked contrast to the progressive rate related prolongation of A V con duction seen in normal subjects with normal PR intervals or in subjects with prolonged PR inter vals as well as in most patients with shortened PR intervals This lack of PR prolongation or minimal prolongation as seen in these groups in dicate the refractoriness of the bypass tract which is unlike that of the A V node

Castellanos and co workers[3] suggested in their paper that the Wenckebach type of increase which is a small increase initially and a plateau response is due to the refractoriness of the bypass tract initially and at higher pacing rates the bypass tract becomes effectively refractory The atrial impulses thereafter are conducted by way of the normal A V nodal pathway which in turn accounts for the sudden increase in the A H in terval as noted in Fig 2 A third response of the A V node which closely parallels the normal could be the result of a partial bypass of the A V node Anatomic correlation of a bypass fiber that although electrophysiologically sound has not been verified.

Comparing Figs 6 and 7 from Patient No 10 it can be seen that with atrial pacing near the SA node the A H interval was 90 msec While the patient was in spontaneous tachycardia at the same rate (180) the A H interval was 140 msec

Atrial pacing involves a mechanism which is somewhat different than that observed in exer cise in that the atrial pacing does not activate the various compensatory mechanisms e g sym pathetic stimulation

The last possibility is the effect of the sym pathetic system on these patients As noted by Lown Ganong and Levine[4] twenty years ago this syndrome has a tendency to occur in hy peractive middle aged females who have a non descript history of palpitations Exercise is known to shorten the A H interval as does sym pathetic stimulation

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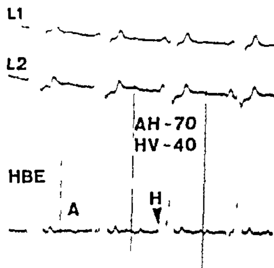


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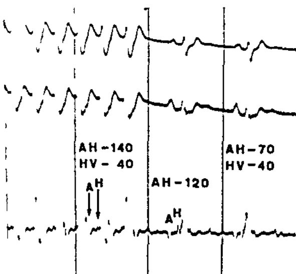


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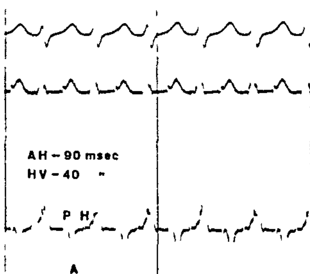


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are more sensitive to, or have excessive sympathetic tone present, enhancing both A V conduction and the possibility of tachyarrhythmias from conducted PAC s and re entry phenomena causing the reciprocating tachycardias Two of the patients with a Type III response were put on a trial of propranolol up to 160 mg daily in divided doses with no change in PR interval, but subjective symptomatic improvement Further clinical testing of this hypothesis is necessary

My appreciation is extended to Dr Richard J McCarty for his guidance and encouragement.

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Serum digoxin levels using an ^{125}I labelled antigen Validation of method and observations on cardiac patients

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William Shapiro M D
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Radioimmunoassay techniques capable of precise measurement of serum digoxin levels are now in common use [1-5] Utilization of the results of these measurements in patient care requires correlation with clinical information and additional studies of digoxin pharmacodynamics [3-6] The purpose of the present study was to evaluate a new prepackaged method of radioimmunoassay and to explore the effects of maintenance dose post alimentary absorption with or without an orally administered diuretic and maximal exercise on serum digoxin levels

Methods

Radioimmunoassay Radioimmunoassay (RIA) kits for measurement of digoxin prepared by Schwarz Mann Division of Becton Dickinson have been evaluated and utilized These kits contain standard digoxin digoxin specific antibodies and either ^{3}H digoxin or ^{125}I 3 0 succinyl digoxigenin tyrosine and the necessary reagent solutions The procedure for the ^{125}I derivative is described in detail

Serum samples obtained from patients before or more than six hours after administration of digoxin were used as unknowns Standard curves were prepared using human serum from persons known not to be taking glycosides (normal healthy volunteers) Determinations were performed in duplicate in disposable plastic test tubes (12 × 75 mm) One milliliter phosphate buffered saline was added to 50 μl serum for use in a standard curve or assay of an unknown Nonradioactive digoxin in concentrations of 0 0 2 1 2 3 5 and 8 ng /ml of serum was added to the calibration tubes Ten microliters of ^{125}I antigen and 10 μl digoxin specific antibody were added to each tube and after shaking the tubes were incubated for 30 minutes at room temperature After incubation 0 5 ml dextran coated charcoal was added to each tube and the contents thoroughly mixed. After 5 minutes at room temperature the tubes were centrifuged at 2000 r p m for 20 minutes The supernates were decanted into disposable plastic tubes Two additional tubes were prepared by adding 10 μl ^{125}I antigen to 1 5 ml phosphate buffered saline These two tubes representing total counts present were allowed to count sufficient time to accumulate approximately 5000 counts utilizing a Tracer lab gamma/guard.* This counting time was used for the standard and patient samples The percentage of labelled bound digoxin was determined from the ratio of standard or patient counts to the total counts The standard curve was plotted on semilog paper with per cent bound as the linear function Patient values in ng digoxin/ml serum were determined from the standard curve A portion of the assays utilized digoxin specific antibodies kindly supplied by Dr James Doherty of the University of Arkansas School of Medicine Little Rock Ark

From the Departm nts of Internal Medicin and Phys logy Univ r sity f T xas H alth Sci nce Ce te at Dallas nd th Cardiovascula Section, Med cal Servic Veter ns Administration Hosp tal, Dall s, Texas.

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Rec i d fo p bl at on April 29 1974

Reprint equests to Willi m Shap ro M.D Chi f Cardiovascul r Section, V te ans Administratio Hosp tal, 4500 South La caste Rd. Dallas, T as 75216

*Se ral k ts ki dly pplied by Schw rz M nn, Orang burg N Y

Manufactured by Divis on of Laboratory for Electr n cs Inc W l tham, Mass

Table I Results of replicate assays on 11 samples*

Sample	% bound			Actual concentration ng /mL	Calculated concentration ng /mL
	Mean	S.D	C.V (%)†		
1	26 6	1 87	7 0	1 75	1 80
2	27 3	1 80	6 6	1 50	1 55
3	24 1	1 95	8 0	2 50	2 55
4	23 4	0 38	1 6	2 50	2 45
5	19 9	0 49	2 5	3 00	2 90
6	10 8	0 29	2 7	5 00	5 00
7	25 0	0 11	0 4	2 00	1 95
8	35 9	0 43	1 2	1 00	1 05
9	19 3	0 85	4 4	Pt A	2 5
10	36 7	1 40	3 8	Pt B	0.36
11	22 5	1 46	6 5	Pt C	2 9
Mean	—	—	4 06	—	—
± S E	—	—	0 790	—	—

*10 replicates per sample
†coefficient of variation

Patient studies *In order to correlate serum* levels with dose venous blood and relevant clini cal data were collected from 356 patients taking various daily doses of digoxin and from 14 pa tients known not to be taking any digitalis glycosides

Postabsorptive studies were carried out in two groups of nine male patient volunteers The first group of nine mean age 57 years (range 44 to 79 years), had been taking 0 25 mg digoxin per day for chronic heart failure secondary to ischemic heart disease and had normal sinus rhythm Ap proximately one hour before breakfast a control Lead II electrocardiogram and a venous blood sample were obtained immediately before a 0 25 mg digoxin tablet (Burroughs Wellcome) was in gested Blood samples and Lead II recordings for rate and rhythm were taken hourly for 6 hours and then again at 24 hours, immediately before the next morning s digoxin dose A second group of nine male patients mean age 57 years (range 48 to 62 years) was similarly studied. These pa tients had the same diagnoses but required 0 25 mg digoxin and a thiazide diuretic daily for maintenance of optimal clinical status Eight of these patients were taking trichloromethiazide 4 mg /day, and one was taking hydrochlorothiazide 50 mg /day This medication was given at the same time as the digoxin Blood urea nitrogen and serum electrolytes were measured at 0 6 and 24 hours in most of these 18 patients

The effects of a symptom limited graded bicy cle exercise test on serum digoxin levels were studied in 16 male patients undergoing evalua tion of their cardiovascular status who had been maintained on 0 25 mg digoxin per day orally Venous blood samples were drawn immediately before and at the conclusion of their maximal ex ercise effort These patients were exercised in 4 minute stages beginning with a work load of 150 kpm and increasing by 150 kpm increments. Rest periods between work loads were 5 to 10 minutes These tests were discontinued when the patient developed chest pain, ischemic ST seg ment changes, extreme fatigue or arrhythmias The pulse rate recoveries were recorded during the first half of each minute of the rest period following each level of exercise These observa tions during and following exercise required an average of 1 hour Heart rate recoveries from the highest level of exercise achieved were then com pared to a group of 16 patients not taking digitalis glycosides but otherwise matched for age maximal heart rate and diagnosis

Results

Comparison of antigen labels Calibration curves and patient samples determined by use of both ^{3}H and ^{125}I labelled digoxin derivatives were compared. A total of 82 calibration curves utiliz ing the ^{3}H digoxin technique were compared with 56 calibration curves utilizing the ^{125}I digoxin technique and found to be statistically identical A total of 92 serum samples from 51 patients

Table II Results of replicate counts on 28 samples*

Sample	*% bound* *Mean*	*S D*	*C V (%)†*	*Counts‡*	*P E (%)§*
1	19 5	0 56	2 9	1950	2 3
2	20 3	0 72	3 5	2000	2.2
3	20 3	2 02	9 9	2000	2.2
4	18 6	0 73	3 9	1900	2 3
5	19 8	0 70	3.5	2000	2 2
6	18 8	0 93	4 9	1900	2 3
7	17.5	0 56	3.2	1750	2 4
8	19 2	0 40	2 1	1900	2 3
9	19 0	0 72	3 8	1900	2 3
10	23 8	0 44	1 8	2400	2 0
11	26 2	0 77	2 9	2600	2 0
12	29 4	0 74	2.5	2900	1 9
13	21 6	0 72	3 3	2200	2 1
14	23 9	0 55	2 3	2400	2 0
15	23 3	0 69	3 0	2300	2 1
16	23 1	0 70	3 0	2300	2 1
17	23 3	0 48	2 1	2300	2 1
18	22 1	0 49	2.2	2200	2 1
19	21 4	0 37	1 7	2100	2 2
20	21 2	1 68	7 9	2100	2 2
21	24 8	0 53	2 1	2500	2 0
22	19 9	1 98	9 9	2000	2 2
23	22 5	0 38	1 7	2250	2 1
24	22 9	0 59	2 6	2300	2 1
25	24 1	0 77	3 2	2400	2 0
26	48 0	0 78	1 6	4800	1 4
27	36 0	0 36	1 0	3600	1 7
28	40 2	0 50	1 2	4000	1 6
Mean	—	—	3 34	—	2 09
± S E	—	—	0 429	—	0 041

*10 epl c te counts per sample
†Coefficient of ariat n
‡Average counts per minute
§Probable error

taking various doses of digoxin and 6 samples from patients not receiving any glycoside were assayed by both techniques The mean digoxin levels for the 2 groups were 0 70 ng /ml with ^{3}H and 0 64 ng /ml with ^{125}I Testing for t value for significance between two sample means revealed no significant difference between these means [7] A linear regression with ^{3}H on the abscissa gave a regression line of $x = 0\ 954\ y + 0\ 087$ with an r value of 0 978 The method utilizing the ^{125}I label required less counting time because there was no need to account for quenching and fewer technical manipulations

Variability of method Both technician and counting consistency were evaluated in order to determine in this laboratory the precision obtainable with the commercial kit materials utilizing the ^{125}I derivative as the antigen For determination of technical error eight different pools of sera with known concentrations of digoxin added and three separate samples of patient sera were utilized. Digoxin concentrations in the eight samples with known amounts ranged between 1 0 and 5 0 ng /ml individual concentrations were 1 0 1 5 1 75 2 0 2 5 (2) 3 0 and 5 0 ng /ml The three patient sera ranged between 0 3 and 3 0 ng /ml Each of the 11 sera was divided into 10 aliquot portions for assay All 10 replicates were assayed simultaneously on the same calibration curve Mean per cent bound ± 1 standard deviation was determined for each 10 replicate set and from this the coefficient of variation (S D /mean) was calculated Coefficients of variation ranged from 0 4 per cent to

Table III Mean serum values for patients on various daily doses of digoxin

	No digitalis	*0 125 mg /day*	*0 25 mg /day*	*0 5 mg /day*	*Intoxication*
Number of patients	14	56	275	25	31
Mean	0	0 80	0 93	1 35	3 86
S D	0	0 44	0 51	0 47	1 40
P values for group comparison			< 05	< 001	< 001

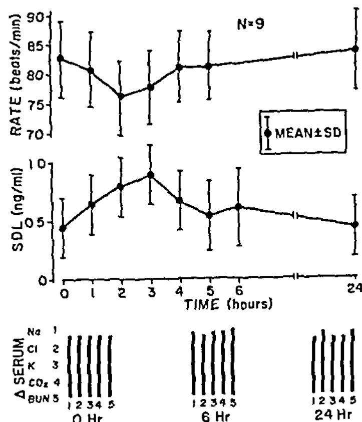


Fig 1 Mean heart rate serum digoxin level (*SDL*) and changes in serum electrolytes and blood urea nitrogen (*BUN*) in nine patients following administration of a 0 25 mg tablet of digoxin See text for discussion

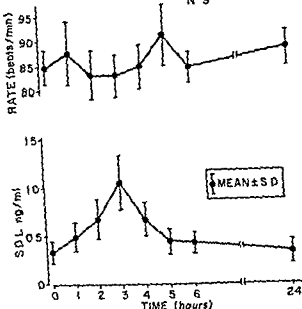
8 0 per cent, and the mean variation for all 110 tubes was 4 1 per cent (Table I)

For determination of counting error a total of 28 serum samples with concentrations between 0 and 3 ng /ml were assayed Each tube was placed in the counter and counted 10 times The coefficient of variation for each 10 count set ranged from 1 3 per cent to 10 per cent and the average variation for gamma counting was 3 3 per cent The expected counter variability, calculated by using the factor for computing probable error ($1/\sqrt{n}$) with n representing total counts present, should average 2 1 per cent for the range of counts present in these determinations The data for determinations of counting error are shown in Table II

Under these circumstances, the bulk of the variation was accounted for by the gamma counting procedure while technical manipulations resulted in a mean error of less than 1 per cent

Clinical tests Fourteen patients assayed who were not taking digitalis had levels of 0 ng /ml with no false positive results Fifty six patients maintained orally on 0 125 mg digoxin per day had a mean serum digoxin level (SDL) of 0 80 ± 0 44 (S D) ng /ml Two hundred seventy five other patients taking 0 25 mg digoxin per day had a significantly higher mean of 0 93 ± 0 51 ng /ml ($p < 0\ 05$) A total of 25 patients receiving 0 5 mg digoxin per day had a mean SDL of 1 35 ± 0 47 ng /ml (Table III) The mean value of this group of patients was significantly higher than those on lower doses ($p < 0\ 001$) Thirty four patients with electrocardiographic evidence of intoxication and with a normal serum potassium had a clearly higher mean digoxin level of 3 86 ± 1 4 ng /ml ($p < 0\ 001$) when compared to the group taking 0 5 mg per day who had no evidence of intoxication

Postabsorptive studies The mean data from the nine patients maintained of 0 25 mg digoxin per day without a diuretic are presented in Fig 1 The serum digoxin level was found to peak at three hours and the 24 hour sample was nearly identical to the mean control level Mean serum electrolytes and blood urea nitrogen (BUN) remained within normal limits at each testing period The decline in pulse rate at two and three hours was significantly below the control rate ($p < 0\ 02$)



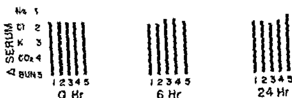


Fig 2 Mean heart rate serum digoxin level (*SDL*) and changes in serum electrolytes and blood urea nitrogen (*BUN*) in nine additional patients following administration of a 0 25 mg tablet of digoxin and a thiazide diuretic The 24 hour value for serum potassium was significantly reduced but within the normal range See text for discussion.

Fig 2 presents the data from the second group of nine patients who were receiving digoxin and a thiazide diuretic The initial values and magnitude of the rise and fall of the serum digoxin levels were similar to those seen in the non diuretic group The peak serum level was again seen at three hours and the 24 hour value approximated control. The BUN and electrolytes did not fall outside the normal range although the serum potassium declined at 6 hours The same general slowing and recovery of the pulse rate was observed, although the changes in rate were not statistically significant

Effects of maximal exercise Fig 3 presents the serum digoxin levels determined before and immediately after maximal bicycle stress testing The mean SDL was 1 0 ng /ml before exercise and 1 1 ng /ml after exercise this was not a significant change Fourteen of the 16 patients showed little alteration in their pre and postexercise values while 2 patients showed increases of approximately 1 0 ng /ml in their SDL s. Fig 4 presents the mean heart rate recovery data for the 16 patients on digoxin and the essentially identical data from the matched group not taking any glycoside

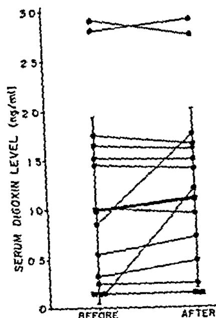


Fig 3 Individual and mean changes (*heavy bar*) in serum digoxin level after maximal bicycle ergometer exercise See text for discussion.

Discussion

Radioimmunoassay has been established as a reliable method for the measurement of digoxin in serum [1-6] Initially the method was developed and widely applied utilizing ^{3}H digoxin as the labelled antigen [1] The present data show the ^{125}I labelled 3 0 succinyl digoxigenin tyrosine to provide equivalent accuracy with a simpler shorter method. The ^{125}I technique may be the superior one when dealing with hemolyzed blood samples patients with bilirubinemia and other similar situations in which color quenching has been reported to give falsely elevated digoxin levels when assayed by liquid scintillation counting techniques [6] The results of the present study demonstrate that the kits tested were adequate for both clinical and investigative purposes The assay was capable of detecting serum digoxin

Table III Mean serum values for patients on various daily doses of digoxin

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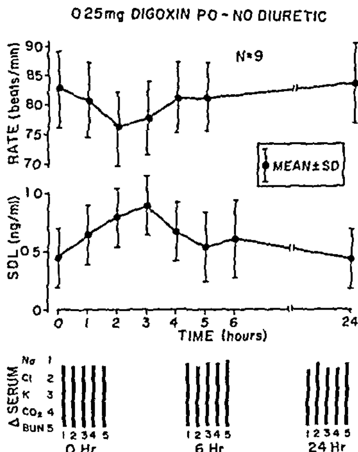


Fig 1 Mean heart rate serum digoxin level (*SDL*) and changes in serum electrolytes and blood urea nitrogen (*BUN*) in nine patients following administration of a 0 25 mg tablet of digoxin See text for discussion

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Table IV *Mean serum digoxin levels associated with commonly administered dosage schedules*

Reference	*Oral digoxin/day*	*Mean ± SD (ng/mL)*	*Number of patients*
1	0.25	1.1 ± 0.3	10
	0.5	1.4 ± 0.4	11
10	0.125	0.5 ± 0.2	5
	0.25 0.375	0.9 ± 0.4	21
	0.5	1.5 ± 0.4	31
11	0.125	0.9	3
	0.25	1.14 ± 0.91	17
	0.50	1.86 ± 1.23	37
12	0.26 ± 0.09	1.0 ± 0.5	62
13	0.125	0.9	3
	0.25	1.2 ± 0.84	29
	0.50	1.42 ± 0.68	
14	0.25	0.83 ± 0.06 (SEM)†	49
	0.50	1.3 ± 0.14 (SEM)	18
15	≃0.25	1.0 ± 0.7	47
Present study	0.125	0.8 ± 0.44	56
	0.25	0.93 ± 0.51	275
	0.50	1.35 ± 0.47	25

Standard deviation
†*Standard error of mean*

not taking digitalis glycosides This implies normalization of reflex control of heart rate compared to that reported in untreated patients [18]

Summary

1 Determinations of serum digoxin levels utilizing commercially available kits with an ^{125}I labelled antigen were precise and not materially different from results obtained with a ^{3}H labelled antigen

2 In order to approximate the steady state level serum digoxin levels should be drawn either before or at least six hours following the administration of an oral tablet.

3 Concomitantly given thiazide diuretics did not interfere with the absorption of a tablet of digoxin

4 In the digitalized patient, slow alterations in serum levels after oral administration appeared well correlated with at least the negative chronotropic effects of the drug

5 Maximal exercise testing a maneuver often applied to cardiac patients does not significantly alter the serum digoxin level

The authors wish to thank Ms Snowie Brown and Ms. Edith K Russell for their invaluable technical assistance

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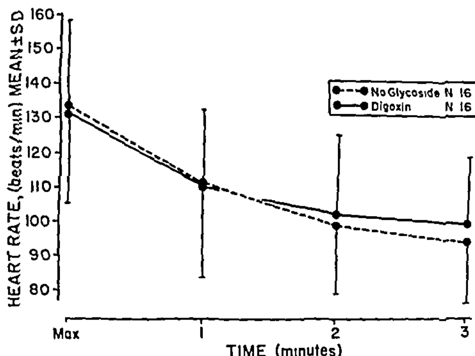


Fig 4 Comparison of mean heart rate recovery after maximal exercise in two groups of patients of similar age disease and maximal attained pulse rate Solid line—16 digitalized patients interrupted line—16 patients not taking digoxin See text for discussion

levels of 0 2 ng /ml Stoll and colleagues[9] have modified the method to detect levels as low as 0 08 ng /ml The average coefficient of variation, due mostly to counter variability was about 4 per cent Others have obtained similar variation with the commercial radioimmunoassay technique[8]

When applied to patient sera, no false positive results were obtained The magnitude of mean serum levels found in patients was related to the size of their maintenance doses The present data and that from several previous studies are presented in Table III[1,10,15] The present postabsorptive studies in contrast to others[16] were carried out in cardiac patients who were given their tablet of digoxin after breakfast, either with or without a prescribed diuretic medication according to usual hospital routine in this institution Initial serum digoxin levels were all within the therapeutic range and returned nearly to control at six hours The single 0 25 mg tablet in these chronically treated patients maintained the initial serum value for 24 hours There was no significant difference between the postabsorptive curves in the group taking diuretics compared with the group not taking diuretics Concomitant electrocardiographic tracings demonstrated slowing of the pulse rate at the time of the highest serum digoxin level, which was three hours after ingestion of the digoxin tablet This was in contrast to the inverse correlation seen between heart rate and serum digoxin levels during the four hours following acute intravenous administration prior to plasma tissue equilibration[6,17] Thus in previously digitalized patients the slow rise and fall of serum levels after oral ingestion of the maintenance dose appears to be positively correlated with at least the chronotropic effects of the glycoside Further a simultaneously administered thiazide did not interfere with or alter the pattern of absorption although correlation with pulse rate slowing was not clear in this group

Maximal exercise had no significant effect on mean serum levels Two patients did show elevations within the therapeutic range (less than 2 ng /ml) following exercise This may have been a manifestation of the postabsorptive rise since these patients were tested at variable periods after their morning dose of digoxin It is noteworthy that in these patients with normal sinus rhythm pulse rate recoveries were no different when compared to a group matched with respect to age disease and maximal achieved heart rate

Case reports

Variant angina pectoris

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In 1959 Prinzmetal and colleagues[1] described a variant form of angina pectoris characterized by chest pain at rest unrelated to exertion and an electrocardiographic (ECG) current of injury pattern during attacks Occlusion or spasm of a major coronary artery with a markedly narrowed atherosclerotic lumen was postulated as the cause of the syndrome

We report here a patient with the characteristics of this variant form of angina pectoris apparently due to a pedunculated calcific mass extending from the aortic valve and resulting in intermittent obstruction of the orifice of the left coronary artery Coronary angiography did not demonstrate any significant atherosclerotic disease

Case report

A 57 year old truck driver was admitted to The New York Hospital complaining of episodic left anterior chest pain of two years duration occurring with increasing frequency over the last three months The pain appeared almost every day usually at rest and often with radiation into the jaw Assumption of upright posture appeared to relieve the pain The rest of his medical history was unremarkable

Physical examination revealed a well developed man with a blood pressure of 120/70 mm Hg and a heart rate of 72 beats pe *minute* The jugular venous pressure was not elevated and the carotid pulse was regular but slow rising The left ventr cle was not enlarged clinically and there was no thrill A harsh systolic ejection murmur (Grade 2/6) and a prominent fourth heart sound were heard along the left sternal border

Laboratory data The hemoglobin was 14 4 grams per 100 ml the leukocyte count was 4 700 per cubic millimeter *with* a normal differential and the serum electrolytes were within normal limits. Multiple determinations of serum creatine phosphokinase and glutamic oxalate transaminase were consistently within the normal range

A chest roentgenogram on admission showed a calcific aortic valve but no evidence of left ventricular enlargement The ECG on admission revealed sinus rhythm with a normal QRS axis and no ST T wave abnormalities

Hospital course A 10 hour ECG test tape demonstrated two attacks characterized by marked ST segment elevation preceded by peaked T waves and followed by recurrent *three second* episodes of tachycardia (Fig 1) Each attack lasted approximately two minutes Neither episode was noted clinically

The patient was transferred to the coronary care unit where hemodynamic data were obtained. Pressures were measured through a Swan Ganz catheter placed in the main pulmonary artery and a No 8 Nylon catheter introduced into the aorta by the Seldinger technique Zero reference point was taken as 10 cm below the sternum Statham P23Db strain gauges were used and recordings were made on an Electronics for Medicine multichannel recorder and a high fidelity magnetic tape ECG Leads I II III *and* V_3 *were* recorded simultaneously At rest the pulmonary artery pressure was 22/11 mm Hg and the central aortic pressure was 104/66 mm. Hg During chest pain there was marked elevation of the ST segments in Lead V_3 only and this was associated with elevation of the *pulmonary artery* pressure to 31/17 mm Hg (Fig 2) Aortic pressure and heart rate did not change significantly during attacks of chest pain

The patient was treated with bed rest and 160 mg of oral propranolol per day A temporary transvenous demand pacemaker was inserted because of sinus bradycardia secondary to propranolol th rapy

The patient experienced several episodes of chest pain associated with ST segment elevation in the precordial leads and frequent tachyarrhythmias both supraventricular and ventricular one episode *required D C* cardioversion On the twelfth hospital day cardiac catheterization was performed. The aortic valve was found to be calcified and an aortogram revealed it to be bicuspid and stenotic The simultaneous mean systolic grad ent across the valve was 23 mm Hg Coronary arteriography revealed normal coronary arteries

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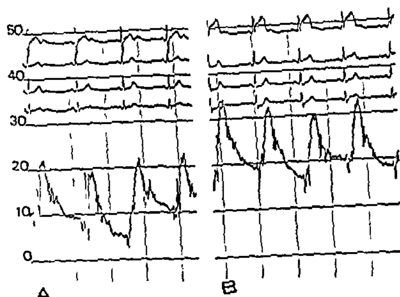


Fig 2 Simultaneous pulmonary artery pressure recordings together with ECG Leads V_3 I II and III A At rest no significant ST segment elevation is noted the pulmonary artery pressure is 22/11 mm Hg B During chest pain marked elevation of ST segments is seen in Lead V_3 *only* the pulmonary artery pressure has risen to 31/17 mm Hg



Fig 3 A Selective left coronary arteriogram in the right anterior oblique projection Note that the vessels are normal and that the origin of the circumflex coronary artery is very proximal B Selective circumflex coronary arteriogram seen in the left anterior oblique projection and showing a normal vessel The right coronary artery was also entirely normal

extensive review of the x ray films The aortic valve was calcified and bicuspid but did not appear to account for the symptomatology as the pressure gradient across it was small in the face of a normal cardiac output and there was no evidence of left ventricular hypertrophy on either ECG or cineangiogram The pedunculated mass of calcium extending from the aortic valve was obviously obstructing the left coronary ostia and presumably in certain positions caused total occlusion and symptomatology Although it appears probable that removal of the calcium mass alone would have resulted in relief of symptoms the surgeon elected to remove the entire aortic valve and replace it with a prosthetic one and to date no symptoms have recurred

Summary

A patient with variant angina pectoris due to a pedunculated calcific mass extending from the aortic valve and resulting in intermittent obstruction of the left coronary ostia is reported

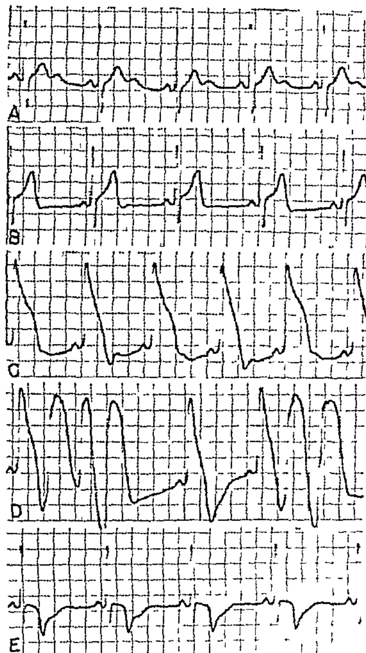


Fig 1 Noncontinuous ECG of patient during attack *A* No abnormalities seen *B* peaked T waves are noted with some ST segment elevation *C* marked ST segment elevation *D* episodes of tachycardia probably ventricular in origin *E* T waves are now inverted

although the circumflex and left anterior descending arteries appeared to originate separately (Fig 3) A left ventriculogram was normal Three days later the coronary angiogram was repeated and again demonstrated normal coronary arteries

Operative findings On the sixteenth hospital day cardiac surgery was performed All three coronary arteries appeared normal and there was no ostial stenosis seen The aortic valve was bicuspid and calcified and had a pedunculated calcific mass protruding from the left coronary cusp and intermittently obstructing the left coronary ostia (Fig 4) The left main coronary artery divided almost immediately into the circumflex and anterior descending branches The aortic valve was excised and replaced with a Smeloff Cutter prosthesis

One year postoperatively the patient was remarkably well with no attacks of chest pain or tachyarrhythmias

Discussion

The diagnosis of Prinzmetal s variant angina pectoris in this patient is based on the typical clinical findings of rest pain not elicited by exercise dramatic ST segment elevation over the anterior precordium during attacks in an area supplied by the left anterior descending coronary artery and associated frequent disturbances of cardiac rhythm often requiring antidysrhythmic medication

Guazzi and colleagues[2] performed hemodynamic studies on four patients with this form of angina pectoris demonstrating a reduction in cardiac output and systemic arterial pressure in association with an elevation of right atrial pressure during attacks They attributed these findings to significant left ventricular dysfunction Our patient demonstrated slight increases in pulmonary artery pressure at the time of ST segment elevation but these changes were not nearly as striking as those we have observed in many patients with the usual variety of decubitus angina pectoris[3] We were unable to demonstrate any circulatory changes preceding the ECG abnormalities in this patient and moderate doses of oral propranolol were unsuccessful in reducing the frequency of attacks as has been reported by others[4]

The etiology of the syndrome in this patient is to our knowledge unique Based on limited pathological material Prinzmetal postulated that temporary occlusion or spasm of a single major coronary artery with a markedly narrowed atherosclerotic lumen was the cause of this entity[5] The technique of coronary arteriography has aided our understanding of the pathophysiology of variant angina pectoris, but to date only 22 cases have been reported with anatomical findings[6,7] In the majority of these cases a focal stenotic lesion of a major coronary artery was found but two recently reported cases raise new doubts about the pathogenesis of this syndrome Both Whiting and colleagues[8] and Ginelly and associates[9] reported patients with variant angina pectoris that could not be explained by significant coronary atherosclerosis

In our patient we were unable to demonstrate any focal stenotic lesion of the major coronary arteries despite two coronary angiograms and

Thymoma masquerading as congenital partial absence of the left pericardium*

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The thymus gland is located in the anterior portion of the superior mediastinum. The differential diagnosis of an enlarged mediastinum must include thymoma which occurs in approximately 10 per cent of patients with *myasthenia gravis*[1] Classically the thymoma is seen roentgenographically as an arch like density base downward above and overlapping the great vessels or it may appear as a well delineated triangular density along the right hilum Presented is a young man who on routine roentgenogram demonstrated an irregularity along the left heart border characteristic of partial absence of the left pericardium Exploration of the left chest demonstrated a large thymic tumor anterior and adjacent to the left heart border The importance of including thymoma and partial absence of the left pericardium in the differential diagnosis of abnormalities of the left heart border as seen on routine roentgenograms is discussed.

Case report

A 21 year-old Navy man presented to the San Diego Naval Hospital with a six month history of progressive weakness dysphagia and diplopia The thymus gland had been irradiated during infancy because of repeated respiratory problems

Physical examination of the cardiovascular system was normal Neurologic examination revealed bilateral ptosis with paresis of cranial nerves III IV and VI There was weakness of the shoulder girdle muscles bilaterally with mild weakness of dorsiflexion of the feet

The electrocardiogram was normal Roentgenographic examination demonstrated an irregularity of the left heart border in posterior anterior projection that could not be seen clearly on lateral projection (Fig 1) Oblique projection demonstrated the irregularity to be anterior in location

The initial test with Prostigmin produced equivocal results. Cardiology consultation was obtained because of the abnormal roentgenogram Experience with congenital partial and complete absence of the left pericardium at the San Diego Naval Hospital has been reported elsewhere [2] Because of the striking similarity of the present case to a documented case of partial absence of the left pericardium (Fig 2) it was judged appropriate to subject the present case to right heart catheterization Fluoroscopic examination showed that the irregularity of the left heart border appeared to move synchronously with each heart beat A pulmonary arteriogram with follow through on levophase showed the mass to be extracardiac

A left thoracotomy demonstrated a pedunculated mass of soft tissue measuring 15 5 by 7 5 by 5 0 cm. and weighing 165 grams overlying the anterior portion of the left pericardium which extended to the thoracic inlet (Fig 3) Microscopic sections revealed a benign thymoma lymphoid type The left pericardium was intact

Discussion

When partial absence of the left pericardium includes herniation of the left atrial appendage an unusual protruding shadow along the left heart border is produced as in the present case The physical examination and electrocardiogram are not helpful since they are usually normal Demonstration of this entity includes opacification of the left atrium showing the herniation of the left atrial appendage beyond the left heart border (Fig 2) In the present case the left atrium and appendage were normal upon

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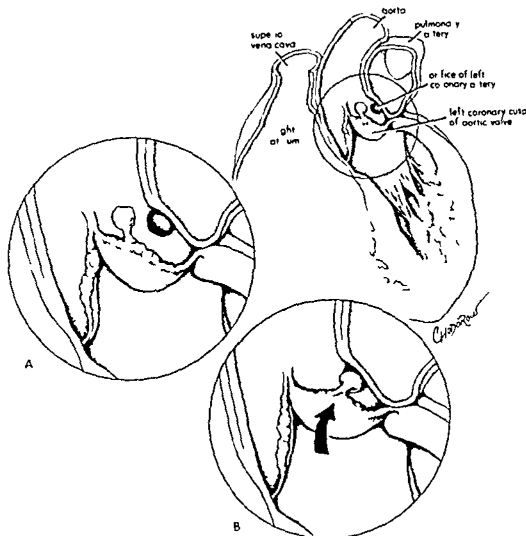


Fig 4 Schematic diagram of operative findings Note that the aortic valve is bicuspid and calcified with a pedunculated calcific mass protruding from the left coronary cusp *A* Enlargement to illustrate that when the patient was asymptomatic there was no obstruction of the left coronary ostia *B* Occlusion of the left coronary ostia by the calcific mass resulting in variant angina pectoris

No atherosclerotic disease was demonstrated by coronary angiography During attacks marked ST segment elevation and episodes of tachycardia were associated with a moderate rise in pulmonary artery pressure Replacement of the calcified aortic valve resulted in total relief of symptomatology

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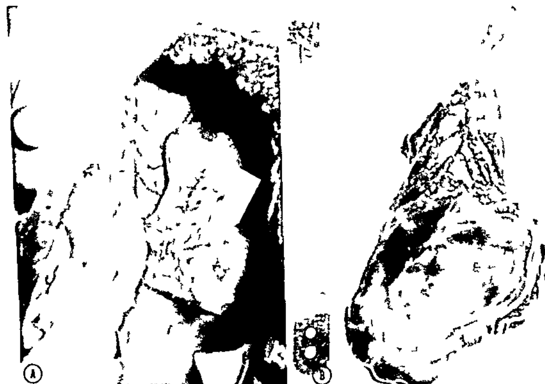


Fig 3 A and B. A Left thoracotomy demonstrating thymoma (*arrow*) anterior and leftward of the left heart border B Gross specimen following removal measuring 15 5 by 7 5 by 5 0 cm and weighing 165 grams.

opacification Thoracotomy revealed an unusually placed thymoma to be the cause of the irregularity along the left heart border Thus congenital partial absence of the left pericardium and thymoma must be included in the differential diagnosis of abnormalities of the left heart border

Summary

Interpretation of irregularities of the left heart border on routine posterior anterior and lateral roentgenograms may be quite challenging Partial absence of the left pericardium provides a characteristic abnormality of the left heart border Described is a case of a thymoma which mimicked partial absence of the left pericardium on routine roentgenography The importance of including both partial absence of the left pericardium and thymoma in the differential diagnosis of irregularities of the left heart border is discussed.

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Fig 1 A and B A Posterior anterior roentgenogram and B lateral roentgenogram in a 21 year old man with a thymoma causing an irregularity of the left border Oblique projections demonstrated that the mass was anterior Note that the mass cannot be seen on lateral projection



Fig 2 A and B A Posterior anterior roentgenogram of a 28 year old man with partial absence of the left pericardium Note the prominent left atrial appendage B Levophase of a pulmonary arteriogram demonstrating opacification of the left atrium left ventricle and aorta. Note the protrusion of the left atrial appendage beyond the left heart border (From Morgan J R Rogers A K and Forker A D Congenital absence of the left pericardium Clinical findings Ann Intern Med. 74 370 376 1971 Used with the permission of the publishers)

not essential for the development of hypertension [4] Immunosympathectomy decreases blood pressure in both Okamoto[5] and New Zealand[6] rats in a somewhat greater proportion than in normotensive rats but it does not prevent a marked increase in blood pressure as the animal matures Adrenal medullectomy does not decrease blood pressure in the Okamoto strain [7]

Hexamethonium has been widely used to produce an acute blood pressure decrease in spontaneously hypertensive rats [6 8 10] but this data may not confirm an exaggerated neurogenic arterial vasoconstriction for several reasons One is that hexamethonium also decreases blood pressure in experimentally hypertensive animals where increased sympathetic activity is most probably not involved [8 11] Second the primary hypotensive potency of hexamethonium results from severe depression of cardiac output peripheral resistance changes little following administration of the drug [9]

Data from environmental experiments support sympathetic involvement in spontaneous hypertension Spontaneously hypertensive rats have been shown to have an increased cardiovascular reactivity to irritating stimuli [2,12] while on the other hand, chronically maintaining the animals in a quiet dark environment slows the development of the hypertension [13]

A theory that reconciles this variety of data is that increased sympathetic nerve activity in the spontaneously hypertensive rat has a specific pronounced effect on renal function that is greater than any effect on the general vasculature In Okamoto animals direct electrical recordings from the splanchnic nerve[14] and also indirect studies[15 16] have shown splanchnic nerve traffic to be increased up to five times that of control rats The direct anatomic connection between the splanchnic sympathetic trunk and the renal sympathetic nerves suggests that renal function is compromised. At least acutely experiments have shown that sympathetic nerve stimulation markedly decreases sodium excretion[17] increased arterial pressure would be required to re establish salt and water homeostasis

The evidence *in toto* suggests that in the Okamoto and New Zealand strains increased sympathetic activity could cause or exacerbate the hypertension particularly via *depressed* renal function but a possible crucial role of inherent renal dysfunction is definitely not eliminated by this data In contrast in the Dahl strain there is rather convincing evidence that hypertension is caused solely by an intrinsic renal defect

Evidence for an inherent renal defect The crux of kidney transplant protocols is that kidneys are exchanged among spontaneously hypertensive and normotensive animals and subsequent blood pressure changes are noted One preliminary report presumably using the Okamoto strain stated that hypertension did not follow transplantation of the hypertensive kidney [18] In contrast Bianchi and colleagues [19] in a separate strain found that hypertension *did* move with the transplanted kidney Similarly Dahl and Herne[20] have observed that hypertension followed the transplanted kidney when kidneys were exchanged between hypertensive and normotensive animals

There is additional evidence for an inherent renal defect in Dahl s strain of hypertensive rats This strain designated salt sensitive becomes hypertensive when placed on a high salt diet but remains normotensive on a normal diet During normal salt intake and before hypertension has ever developed, Jaffe *and co workers*[21] have observed a mild nonuniform focal constriction of the early afferent arterioles The constriction is not observed in a companion strain of salt resistant animals a strain that remains normotensive on all salt intakes. But in the salt sensitive animals the hypertensive response to high salt diet includes further encroachment of the lesion upon the lumen of the afferent arteriole as if an intrarenal response to the high salt diet was creating a wealth of diffuse minute Goldblatt clamps. Renal blood flow and glomerular filtration rate are normal after the development of hypertension [22] evidence for a considerably elevated renal afferent resistance This alteration in renal morphology and function is irreversible in that hypertension persists after the salt rich diet is discontinued [23]

There is also some indication of renal dysfunction in the Okamoto strain but it may not be due to intrinsic causes. Kidney weight in these animals is normal [2] and no morphologic abnormalities have yet been discovered.[2] Folkow and co workers[24] have measured a *decreased* renal resistance in isolated Okamoto kidneys perfused at low pressure The renal vasculature in these preparations appears abnormally stiff and it may

The role of the kidney in spontaneous hypertension

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Renal dysfunction is critically involved in many forms of human and experimental hypertension Spontaneously hypertensive rats may have a similar defect

Interpretation of recent data is complicated by the fact that many different colonies of spontaneously hypertensive rats have been studied Some are local creations while others are representative of the several more standard strains The Okamoto strain is the best known and most widely disseminated a strain developed by Dahl and colleagues at Brookhaven remains normotensive until subjected to high sodium intake, the New Zealand strain has been distinguished by a less than total incidence of hypertension

Each strain has descended from a single unique pair of animals Because the hypertension that occurs in each of the colonies is the result of an unusual genetic trait in the original animals there is little guarantee that the same specific physiologic mechanisms are involved in each of the different hypertensions For example two different hypothetical groups of animals could develop hypertension one hypertension due to an inherited primary aldosteronism and the other due to an inherited pheochromocytoma Even though comparable elevations in blood pressure were observed and the adrenal glands were known to be intimately involved in both forms of hypertension there would be few additional similarities The unique origins of the different strains now being studied may prevent generalization however, if potential differences among strains are kept in mind several working hypotheses can be examined

Of many possible theories two directly relate primary renal dysfunction to spontaneous hypertension One theory is that increased extrinsic influences upon the kidney particularly from the sympathetic nervous system, cause depressed renal function leading to hypertension A second theory is that intrinsic or inherent renal dysfunction leads to hypertension The point that these two theories have in common is that a renal defect produces elevated pressure almost, as it will be argued later, as if the animals have inherited a diffuse intrarenal Goldblatt clamp The distinction between the two theories is that in the former (increased extrinsic influence) hypertension would be expected to occur even if a recipient animal were given a replacement kidney from a genetically normotensive animal while in the latter (inherent renal dysfunction) hypertension would be expected to follow the kidney in renal transplant experiments

Possible role of the sympathetic nerves There is evidence both for and against the contention that increased sympathetic activity is critically involved in the genesis of spontaneous hypertension with most attention being focused on the Okamoto strain Some variability in sympathetic function and catecholamine stores has been observed,[1,2] but the irregularities do not convincingly account for the increase in pressure especially via arterial vasoconstriction Pfeffer, Frohlich and Pfeffer[3] have identified an increased beta sympathetic state that particularly affects cardiodynamics Increased cardiac stimulation may contribute to the final hemodynamic picture observed but it is apparently

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in the Okamoto strain the resulting rapid elevation in blood pressure is associated with increasing blood volume and extracellular fluid volume[39] Similarly increased extracellular fluid volume has been observed immediately following the implantation of hypertension producing kidneys into normotensive rats[40] In both cases fluid retention coincides with the development of hypertension in a previously normotensive animal Extrapolating from this short term data salt and water retention may be important in the more subtle elevation in pressure that normally occurs

Summary

There is direct and indirect evidence that the kidneys are involved in the onset of hypertension in spontaneously hypertensive animals In the Dahl strain rather convincing evidence exists for a primary inherent renal defect that is worsened by high dietary salt. In the Okamoto and New Zealand strains an intrinsic defect may be provoked by increased sympathetic nerve activity Similarities between all of these strains and Goldblatt hypertension suggest a fluid volume abnormality but the gradual onset of elevated pressure and continuing growth during development of hypertension may obscure critical volume changes Theoretically arterial pressure somewhat independent of intermediate steps will reach the level which is dictated by renal function as being necessary for the maintenance of salt and water homeostasis. While widespread use of different spontaneously hypertensive strains may currently be complicating our understanding of the intermediate steps studies of dissimilar strains should, in time enhance our understanding of the many different facets of long term blood pressure control

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be that at higher perfusion pressures the renal resistance is in fact greater than normal In other studies of Okamoto rats, blood flow through the kidneys *in situ* has been observed to be low[25,26] even at the very high arterial pressures that commonly occur

Similarity between spontaneous and Goldblatt hypertension The blood pressure of Okamoto animals is remarkably insensitive to the level of salt intake, with hypertension developing on both low and normal salt intakes[27,29] Similarly, even though Dahl s strain of rats is called salt sensitive the animals' arterial pressures are remarkably *salt insensitive* after a high salt diet has been administered for a requisite but short, amount of time[23]—the hypertension persists when the animals are subsequently placed on a low salt diet The lack of pressure sensitivity to salt intake in these strains is nearly identical to the Goldblatt clamped rat that has *all* of its renal tissue distal to a renal artery constriction, most commonly the preparation consists of unilateral renal artery clamping in combination with con tralateral nephrectomy

Parallelism between spontaneous and Gold blatt animals is further developed by the ap parent lack of involvement of the renin angiotensin system in both forms of hypertension With Goldblatt clamping, the abrupt application of a clamp provokes temporary renin release but this subsides as the hypertension develops and the pressure distal to the clamp rises toward normal values After the initial transients plasma renin activity is quite normal There is no comparable abruptness in the onset of hypertension of the spontaneously hypertensive rat and this may allow the renin angiotensin system to remain pri marily dormant in these animals

Possible role of fluid volumes Experience with anephric patients has shown that rather small changes in fluid volumes can have a pronounced effect on arterial pressure Similarly, the early sodium and water retention in Goldblatt hyper tension gives way to only the *slightest* of abnor malities in the chronic state In both instances a strong argument can be made for an important role of fluid retention in the onset of hyperten sion, the argument is that overhydration causes an increased cardiac output which in turn trig gers an autoregulatory response[30,31] Demonstra tion of the same sequence of events in spontane ously hypertensive rats has been difficult Fluid volume measurement in Okamoto,[32,33] New Zea land[34] and Dahl[34] rats has not revealed compara ble overhydration There are two critical con siderations (1) absolute fluid volume is important in the circulation only in relation to the com pliance of the vasculature that it is contained in and this compliance may be decreasing as spon taneous hypertension develops and (2) the grad ual onset of spontaneous hypertension may allow very subtle overhydration to play a more impor tant role in elevating pressure than previously sus pected.

The vasculature hypertension vs growth Growth is a physiologic process which demands increased vasculature while hypertension is a disease which produces decreased vasculature Decreased vasculature and therefore increased resistance is probably the result of the physiolog ic response of overperfused tissues[36] and later, pathologic effects[2] The conflict between growth's demands for increased vascularity and the dis ease process might be resolved within the sponta neously hypertensive rat by retardation in the normal development of the animal s vasculature It is interesting to note that these animals do not grow particularly rapidly as if an inadequately developed circulation is not capable of supporting the normal rate of accumulation of body mass

The mature spontaneously hypertensive rat shows a decreased number of arterioles[2,37] and venules[38] when compared to normotensive con trol animals Normal absolute fluid volume plus decreased compliance could equal relative over hydration It is not clear, though if vascular change plays a role in the onset of elevated pressure or if it follows and is caused by the ele vated pressure

Transient volume changes Sudden changes in renal function can produce easily identified in creases in fluid volumes during the onset of hy pertension The spontaneously hypertensive rat does not usually undergo any abrupt changes comparable to those produced by experimental intervention in other animal models e g the sudden decrease in renal function that occurs with renal artery clamping There are two obser vations in spontaneous hypertension however that have been made during abrupt changes in the animal s status and suggest that fluid volume retention may have a direct role in the etiology of this hypertension One observation is that after cessation of successful antihypertensive therapy

Interesting aspects of geriatric cardiology

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Geriatric cardiology has received extremely little attention even though the number of old people in the world is large and is increasing constantly Those physicians who have been interested in geriatric cardiology are primarily concerned with *disease* of the heart in people 65 years of age or older [1-14] However geriatric cardiologists seem to manifest little concern about aging of the heart itself For example does the heart actually age in man i e deteriorate with time independent of organic disease such as coronary artery disease rheumatic fever infections trauma or other acquired lesions? It is well recognized that ischemic heart disease is the most common type of heart disease of old people (Fig 1) [14,15] Because coronary arteriosclerosis develops and progresses with age it is almost impossible to learn whether or not disease or deterioration of the heart develops with age i e merely with the passage of time

We were able to observe marked myocardial changes with age in the *Drosophila* by means of electron microscopy [16] The *Drosophila* has no coronary arteries its myocardium is one cell thick and its normal life span is so short that old *Drosophila* were readily available for study The mitochondria in the myocardium of the old flies showed marked structural changes (Fig 2) Such changes have been reported in the myocardium of old rats[17] and also in mitochondria of their retina [18] Obviously it is not always possible to extrapolate meaningfully such observations to man Nevertheless since such changes occur with age in the myocardium of the *Drosophila*, there is no reason not to expect senescence to be associated with morphologic and functional alterations with age in the heart of man Some of the major alterations noted in the human heart with age are described below

F om the Lou a H rt Ce ter at the Charity Ho p tal New Orle ns a d th Depa tment f Medic n Tula Uni rsity School of Medic e N w O l ns

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Morphologic changes with age

Gross changes Unless there is an etiologic factor responsible for heart disease the heart of an old person remains normal in size or it may actually decrease in size in association with reduction in body size Even though the body reduces in mass and all anatomic structures tend to become smaller with age the heart tends to reduce relatively less in size Old people tend to develop anoxemia and anorexia which result in the senile cachectic state The heart decreases in size and fat mass as cachexia develops The color of the myocardium tends to darken and to become brownish due in part to an increase in the concentration of lipofuscin in the myocardium with age

The endocardium thickens with age The thickening is diffuse with some areas thicker than others This fibrosis with collagen fibers and some elastic fibers is greater in the left ventricle and left atrium than in the two right chambers The fibrosis produces a whitish cast to the inner surface of the heart

The valves also become more fibrotic with age The valve leaflets are thickened and are more rigid than normal This fibrosis is similar to the changes noted in the endocardium and subendocardium The mitral and aortic valves are more involved than the tricuspid and pulmonic valves [9] Calcium may be deposited in the valve leaflets and cusps Calcification is marked at times at the annulus producing an irregular

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Fundamentals of clinical cardiology

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George E Burch M D
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Fig 2 Electron micrograph of section of heart of a 4 month old *Drosophila repleta* showing large quantities of glycogen particles (IG) accumulated within the mitrochondria and circumferential orientation of cristae (arrows) ×43 200 (From Burch G E, Sohal R S and Fairbanks L D Ultrastructural changes in *Drosophila* heart with age Arch Pathol 89 128 1970)

with only heart disease [15] They always display multiple diseases of varying severity each organ diseased or aged to a different extent and to varying degrees among different patients All the changes are related to age in some manner The rate and extent of aging vary among people so that chronologic age can be deceiving Only the master clinician can properly integrate all of these variables each having a different coefficient of magnitude and rate of change and each requiring varying amounts of therapeutic attention For example in addition to the general aging of the entire individual it is not uncommon for the old patient who consults his physician

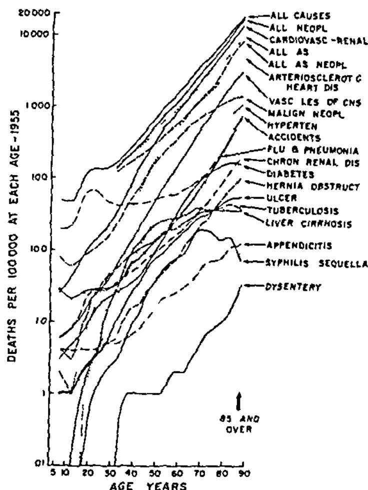


Fig 1 Mortality from selected causes by age (From U.S National Office of Vital Statistics report for 1955) (From Kohn, R R Human aging and disease J Chron Dis 16.5 1963)

rough serrated ring in either or both the mitral and aortic valves The leaflets and cusps may become calcified to a variable extent with age The tricuspid and pulmonic valves are rarely calcified or even markedly thickened by fibrosis in old people It is not known why these fibrotic changes occur in the endocardium or valves They are usually attributed to wear and tear and/or previous injury by infection immunologic phenomena and/or physical trauma As a rule however the morphologic changes are not severe enough to produce significant hemodynamic changes Occasionally there is significant aortic valve stenosis and/or insufficiency and/or mitral valve insufficiency Mitral stenosis due to the aging process alone is extremely rare However when minor hemodynamic changes are superimposed upon underlying organic heart disease the hemodynamic alterations can be serious and produce important clinical differences

Microscopic change Light microscopy has revealed significant increase in collagen and elastic fibers throughout the old heart This finding is most pronounced in the endocardial and subendocardial areas and valves but it occurs throughout the myocardium even involving the conduction tissue to some degree These changes with age of course may reflect the influence of senescence only, i e , senile cardiomyopathy,[19] but they may also reflect associated organic heart disease such as coronary artery disease and disease produced by previous viral and bacterial infections Regardless of the mechanisms involved the changes do occur with age

The myocardial fibers tend to shrink or atrophy in some areas hypertrophy slightly in other areas and even show fragmentation The anatomic changes are certainly sufficient to produce functional disturbances

Physiologic changes with age

The hearts of old people do not pump as well as the hearts of young people The cardiac output and the capacity to work and maintain a vigorous circulation for prolonged periods of time are reduced (Fig 3)[20,21] The magnitude of the capacity to work and produce pumping power varies considerably but progressively decreases with age Any physician has only to watch an old man run, exercise vigorously or exercise for a prolonged period of time to observe what is also happening to his myocardial function as well as to his skeletal muscle Not only does the old man experience palpitation early and to a disturbing degree, but irregularities in cardiac rhythm develop along with dyspnea and cough His myocardial reserve is reduced.

Some of these manifestations may be related to changes in vasomotor tone and vagal tone Peripheral vascular resistance (systemic and pulmonary) is increased in older people over that in the young With arteriosclerosis and a more rigid arterial system in the aged systolic blood pressure is increased (Fig 4 Table I) even more than diastolic pressure [9,22] The increase in contractility and irritability probably are expressions not of the aging process alone but of myocardial ischemia as well Scarring and other degenerative changes produced by previous viral and bacterial infections must cause some of the many changes noted in the hearts of old people

Clinical aspects

Geriatric cardiology is concerned with heart problems in old people Old people *never* present

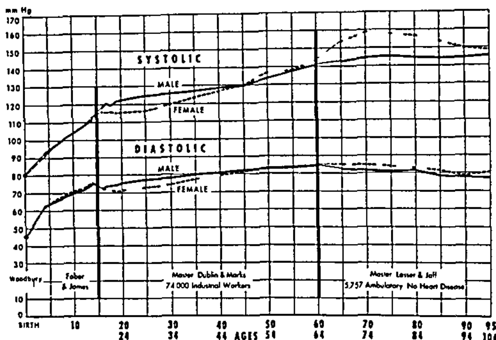


Fig 4 Mean blood pressure levels in apparently healthy people from birth to old age (From Master A M and Lasser R P Blood pressure elevation in the elderly *In* Hypertension Recent Advances Brest A N and Moyer J H editors. Philadelphia 1961 Lea & Febiger pp 24 34)

Table I Mean blood pressure in adults by age and sex 1960 62 (mm Hg)

Age	*Men*			*Women*		
	No	*Systolic*	*Diastolic*	*No*	*Systolic*	*Diastolic*
18–24	7 139	121 7	71 6	8 430	111 8	69 4
25–34	10 281	124 7	76 4	11 291	115 6	72 9
35–44	11 373	128 6	80 7	12 325	122 8	78 0
45–54	10 034	133 8	83 2	10 54[illegible]	133 8	82 0
55–64	7 517	140 3	83 1	8 121	146 6	84 9
65–74	4 972	148 0	81 0	6 192	160 2	83 7
75–79	1 428	154 3	79 4	1 443	156 6	79 3

N tional Cente f He lth Statist cs Seri 11 No 4 1964
(From H rris, R. The Man g m nt of G ri tr Card o ascular Dise se Ph ladelphia 1970 J B Lippincott.)

especially in women who stand a great deal particularly during warm weather When edema has been a chronic problem the heart should be enlarged if the edema is due to heart disease with congestive heart failure Chronic congestive heart failure does not occur without cardiac enlargement. It is necessary of course to be sure if the heart has enlarged or not It must be remembered however that acute congestive heart failure can occur in association with angina pectoris or myocardial infarction without cardiac enlargement Cor pulmonale with chronic right ventricular congestive heart failure is always associated with an enlarged right ventricle

When the physician is in doubt as to whether congestive heart failure (CHF) or chronic pulmonary disease is producing the dyspnea he can elegantly digitalize[23] his patient with the associated use of diuretics If the symptoms and signs are due to CHF they will disappear or improve with digitalization whereas there will be no change if they are due to emphysema chronic bronchitis, and extracardiac effects of aging The patient will not be injured or subjected to any risks if the precautions noted below in the sec

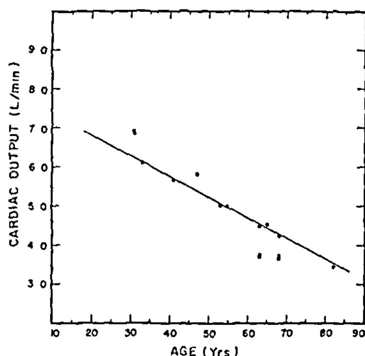


Fig 3 The relationship between cardiac output and age in 67 males without circulatory disorder and during basal" state The line indicates the simple linear regression for the data (From Brandfonbrener M Landowne M and Shock N W Changes in cardiac output with age Circulation 12 557 1955)

about his heart to have at the same time emphysema chronic bronchitis, cholelithiasis hiatal hernia recurrent diverticulitis of the colon prostatic hypertrophy generalized arteriosclerosis arterial hypertension cataracts cerebrovascular ischemia otosclerosis chronic cystitis, hemorrhoids chronic constipation diabetes mellitus and other diseases in varying combinations and extent Thus a physician can be a master cardiologist only if he is also a master internist and general clinician *at all times* The contributing manifestations and interrelationship of all of these illnesses must be considered when evaluating the cardiac status and the patient s symptoms and signs Furthermore such consideration is necessary when outlining management and especially when contemplating hazardous diagnostic and therapeutic procedures The associated illnesses must be managed or at least seriously considered along with the treatment of the heart disease itself

The most important aspect of the clinical study, therefore, is not just the cardiac investigation but the general inventory of the patient's state of health For example, it is essential to treat the patient, not his T waves premature beat or bundle branch block Patients can live many years with these abnormalities, especially if they are not producing symptoms and if the patient s general state of health is properly managed The associated disease or diseases or his age per se may be most important Furthermore unless the physician is careful the therapy itself may cause even more serious cardiac and general difficulties e g, digitalis intoxication steroid reactions accident from coronary angiography and drug reactions of various sorts The physician's clinical decisions are usually difficult to reach and time consuming, but are extremely important

There are many symptoms common to patients with heart disease and also to old people without heart disease A few may be noted

Dyspnea is a common complaint among old people It is often due to chronic bronchitis as a result of tobacco smoking occupational exposure to pulmonary irritants, and/or repeated respiratory tract infections Senile emphysema and chronic bronchial asthma are common among old patients There is impairment of respiratory function with old age as well as impaired use of all skeletal muscles so that dyspnea on exertion is often if not usually present even in the absence of heart disease Old people frequently have relatively insignificant Cheyne Stokes breathing when asleep This often alarms relatives The physician must be sure that the Cheyne Stokes breathing is not due to respiratory cardiac or renal failure This decision is usually easy to make

Weakness and giddiness Patients with heart disease and old people without heart disease experience weakness and giddiness Orthostatic hypotension is a frequent complaint of old people as well as of patients with heart disease The physician must determine the cause of these common complaints Furthermore when heart disease exists in old patients both heart disease and age itself can be contributing factors Unless the physician is alert he may erroneously attribute these symptoms strictly to heart disease and overestimate the seriousness of the cardiac disability Furthermore malnutrition senile anemia (unpublished observations) renal disease and other illnesses frequently encountered in old people may also exist to produce weakness and giddiness

Edema Mild edema of the feet, ankles and lower third of the legs is common in old people

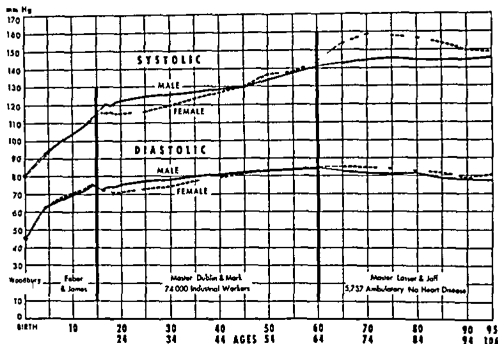


Fig 4 Mean blood pressure levels in apparently healthy people from birth to old age (From Master A M and Lasser R P Blood pressure elevation in the elderly *In* Hypertension Recent Advances, Brest A N and Moyer J H editors Philadelphia 1961 Lea & Febiger pp 24 34)

Table I Mean blood pressure in adults by age and sex 1960 62 (mm Hg)

Age	Men			Women		
	No	*Systolic*	*Diastolic*	*No*	*Systolic*	*Diastolic*
18–24	7 139	121 7	71 6	8 430	111 8	69 4
25–34	10 281	124 7	76 4	11 291	115 6	72 9
35–44	11 373	128 6	80 7	12 325	122 8	78 0
45–54	10 034	133 8	83 2	10 542	133 8	82 0
55–64	7 517	140 3	83 1	8 121	146 6	84 9
65–74	4 972	148 0	81 0	6 192	160 2	83 7
75–79	1 428	154 3	79 4	1 443	156 6	79 3

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When the physician is in doubt as to whether congestive heart failure (CHF) or chronic pulmonary disease is producing the dyspnea he can elegantly digitalize[23] his patient with the associated use of diuretics If the symptoms and signs are due to CHF they will disappear or improve with digitalization whereas there will be no change if they are due to emphysema chronic bronchitis and extracardiac effects of aging The patient will not be injured or subjected to any risks if the precautions noted below in the sec

tions on management are remembered A diuretic, of course cannot help in differential diagnosis

It is not possible to discuss here the many clinical problems associated with geriatric cardiology The above discussions provide a few ideas to convey the concepts involved in the many symptoms and signs of and the difficulties in managing old people with cardiac problems

Management of the geriatric patient with heart disease

Old patients with heart disease can be treated best at home when possible or in a private hospital room with well trained cardiac nurses the necessary monitoring and with members of the family available and nearby Old patients do not tolerate the coronary care units very well unless each room is private and sound proof and the patient well isolated The disturbances associated with dying patients and the activity associated with the management of other seriously ill cardiac patients have serious disturbing effects on old patients especially the cardiac patient who is already seriously ill For the best treatment it is necessary to have well trained nurses and attendants in constant care of the patient The open or semiprivate coronary care unit does not necessarily provide the best conditions for geriatric cardiologic patients

There are certain rules in therapy that should be remembered in geriatric cardiology For example old patients are more sensitive to digitalis than young patients This applies for almost all drugs Experience gained with young cardiac patients must be applied cautiously to older patients If the technique previously described[23] for digitalizing patients is carefully followed, the geriatric patient will not be intoxicated It is always advisable to use smaller doses of digitalis than those used in young adults and to digitalize the patient gingerly

It is imperative to prescribe all drugs cautiously in older people This includes sedatives fluids diuretics blood and many other therapeutic agents Old people tend not only to confuse therapeutic instructions but to forget them and fail to follow instructions properly It is important therefore, when using dangerous drugs such as diuretics digitalis and antiarrhythmic and antihypertensive agents in the management of geriatric patients with such a hazardous disease as cardiac disease, to give the instructions to responsible young members of the family The family and/or attendant should accompany old patients to the physician's office or be present at the bedside when these points or instructions are discussed. The cardiologist must never trust dangerous drugs to patients with cerebrovascular insufficiency or senile dementia The mental state often deteriorates from the cardiovascular disease itself or from reactions to drugs

Greater emphasis must be given to rest, diet, nursing care, bowel care and all general hygienic measures The old patient is most appreciative when the physician is gentle considerate and patient Old patients cannot be treated hurriedly or roughly Cardiac illnesses are serious in all patients but even more serious in old patients Always remember that the life expectancy of old patients is brief because of their age alone

Hypertension impairment of renal function anemia, constipation insomnia, tension and anxiety loneliness malnutrition feeling of being unwanted all contribute to the patient s symptomatology and even to his illness Every little improvement in health that can be achieved can make an important difference in geriatric cardiology The psychic, economic and social states of old people are extremely important factors to consider in therapy It is important that the physician see the patient frequently at home hospital or office since the cardiac state can change rapidly and greatly complications develop suddenly and reactions to drugs occur frequently and rapidly A visit to the home of any patient but especially a visit to an old patient s site of residence is usually most rewarding for proper management and for the accumulation of knowledge about the patient The geriatric cardiac patient needs close supervision and much sympathy and reassurance

Laboratory studies and special procedures

The usual routine laboratory studies should always be included in the cardiologic study EPA and lateral x rays of the heart and lungs electrocardiogram (ECG) complete blood count (CBC), urinalysis stool examination and blood chemistries including uric acid should be routine Hazardous special examinations are rarely if ever necessary and when employed they are

done only with careful and deliberate justifica tions The stress test electrocardiograms are rarely if ever necessary once a careful history and physical examination have been obtained. The stressful treadmill ECG studies are not only unnecessary but dangerous and contraindicated in old people especially feeble old people Until coronary angiography and coronary bypass sur gery are better understood and evaluated it is best not to employ these hazardous procedures in geriatric patients The cardiac pacemaker on the other hand has been of considerable value in the treatment of complete heart block when in troduced properly After all complete heart block is a fairly common and highly fatal disease of old patients

Chest x ray of elderly patients Fig 5 shows a typical teleoroentgenogram of the chest of an old patient Typically the anteroposterior diameter of the chest is increased There is slight to moderate or even marked kyphosis. Osteoporosis is usually present in varying degrees as noted in the thoracic vertebrae and is associated with varying degrees of hypertrophic arthritis of the vertebrae The anterior posterior (AP) view tends to show relatively small lung fields in women Emphysematous changes with relatively flat diaphragmatic shadows are usually evident The lung fields tend to show pulmonary fibrosis along with the emphysema The heart is of aver age normal size or it may even be relatively small unless there is cardiac disease The aorta is un coiled and slightly dilated There may be a semi lunar calcified arteriosclerotic plaque in the aortic knob All these changes tend to be more pronounced in women than in men



Fig 5 Typical chest roentgenogram of an elderly person The patient has arteriosclerotic (ischemic) heart disease

The electrocardiogram in elderly patients Of course the electrocardiograms of elderly patients will reflect disease states of the heart as they do for other patients However when treating elder ly patients the physician is especially concerned about changes in the electrocardiogram that re flect myocardial changes associated with age only and not necessarily any specific type of heart disease He is necessarily concerned about the significance of differences in the ECG of nor mal old people from the ECG of normal young people He is constantly confronted with the problems of making decisions of a diagnostic prognostic and therapeutic nature in elderly pa tients, even in those who consult him for periodic health examinations The cardiologist is fre quently asked to see old patients with electrocar diograms considered abnormal for young people and to advise about diagnosis and management. For example are old people normal and if they are what are the criteria for a normal ECG of old people? As is true for gray hair and wrinkled skin old people often have low or negative T waves abnormal ST segments and slurring and notching of the QRS complex without other evi dence of cardiac abnormalities Are such changes normal for old people? The data required to answer such questions are not available at pres ent. However physicians have their opinions and experiences and they must make decisions

Efforts have been made to investigate the ECG of normal old people and to decide when the tracing is abnormal There have been a number of reports of a statistical nature[24] which summar ize the ECG findings in people 70 years of age or more (Table II) but many of the subjects have been patients in clinics hospitals and nursing homes Many such subjects must be sick to be there Regardless some of the findings may be summarized as follows

The most frequent change in the ECG with age is alteration in configuration of the ST segment and T wave The ST segment tends to become isoelectric or flattened (Fig 6) The T wave usually changes its configuration with aging (Fig

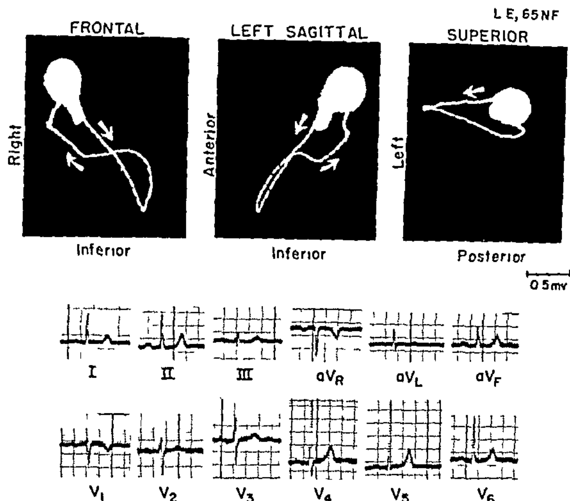


Fig 6 Flectrocardiogram and spatial vectorcardiogram of an elderly patient who had no evidence of heart dis ease The ST segment is typically flattened throughout the ECG and the contour of the T wave differs from that of normal young people The QRS sÊ loop of the sVCG is markedly distorted

6) The upstroke is less gradual, the T wave becomes lower in Leads I, V_5 and V_6 as well as in other leads (Fig 7), and it may finally become diphasic or negative (inverted) Such changes in young people would be considered reflections of abnormalities, often serious This must be true to some extent for old people as well However old people have a shorter life expectancy according to actuarial statistics whereas young people should have a much longer life expectancy But with more years yet to live younger people may have their lives shortened by the myocardial ab normalities reflected in the ST segment and T wave changes, whereas those same myocardial abnormalities may not have sufficient time to in fluence life expectancy in the elderly patient 70 years of age or more who has only a few years yet to live However, diseases tend to progress more rapidly in older people and old people do not withstand disease states as well as younger ones Nevertheless the physician must decide the im portance of the ECG changes and the prognosis If the changes in ST segments and T waves re main stable thev tend to have less significance and less serious prognostic connotations than if they are changing rapidly and especially if they are becoming more abnormal The physician must therefore follow his elderly patients close ly and meticulously to learn the significance of changes in the ST segment and T wave configu rations Such changes are extremely common in elderlv people without other evidence of heart disease Unfortunately there are no generally accepted criteria for the normal ECG in people over 70 years of age The physician must therefore determine the clinical significance of ECG changes for each individual patient

Most studies show heart disease to exist in 10 to 30 per cent and even up to 59 per cent of peo ple over 70 years of age [24] This is two to three times the incidence among people less than 65 years of age Because clinical histories are so

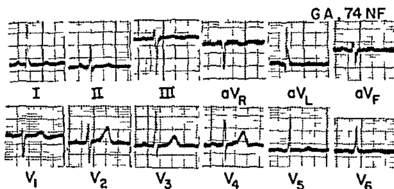


Fig 7 Electrocardiogram of a 74 year-old woman with psoriasis and rheumatoid arthritis showing flattened ST segments and low T waves throughout.

Table II Reported incidence of abnormal ECG clinical heart disease and various ECG abnormalities in old people (Modified from Mihalick M J and Fisch C Electrocardiographic findings in the aged, AM HEART J 87 117 1974)

Entity	*Mihalick & Fisch series (671 subjects > 65 years of age)*		*Other reported series (subjects > 70 years of age)*		
	No with entity	%	*No in series*	*No with entity*	%
Clinical heart disease	331	49	1 801	1 055	59
Abnormal ECG	306	46	2 482	1 411	52
Atrial fibrillation	34	5	2 310	188	8
Abnormal left axis deviation	74	11	1 190	611	51
Right axis deviation	6	1	1 190	14	2
First degree atrioventricular block	67	10	3 145	292	9
Right bundle branch block	54	8	2 037	107	5
Left bundle branch block	33	5	2 037	55	3
Atrial premature systole	71	10	502	49	10
Ventricular premature systole	74	11	502	29	6
ST T changes	128	19	1 435	227	16

unreliable in old people the significance of ECG changes becomes even more difficult to determine Furthermore there is a relatively high incidence of ECG manifestations of myocardial infarctions in old people who are clinically normal. Since hardy people live longer and since the physical demands placed on elderly people are relatively little the prognostic criteria of ECG changes should be expected to differ from those for young people

Mihalick and Fisch[24] found ST segment and T wave changes in the ECG of 16 per cent of 1 435 patients over 70 years of age Nineteen per cent of these had hyperglycemia hypertension and/or obesity In a review of 2 482 patients 70 years of age or older gathered from the medical literature [24] 52 per cent had an abnormal ECG using the usual criteria for a normal ECG (Table II) With such a high incidence one can only wonder if the standards for a normal ECG in old people should be different from those for young people

Prolonged P R intervals are relatively common in elderly people (67 out of 671 individuals) [24] and about 1/3 of them have an associated bundle branch block The R and S waves in Leads I V_5 and V_6 of old people tend to decrease in amplitude and the QRS complex tends to become more prolonged, slurred notched, and deformed in other ways with old age Left axis deviation develops with aging and the axis may become oriented more to the left than −30 This magnitude of left axis deviation is usually associated with left ventricular hypertrophy The transitional zone tends to change in older people because of emphysema

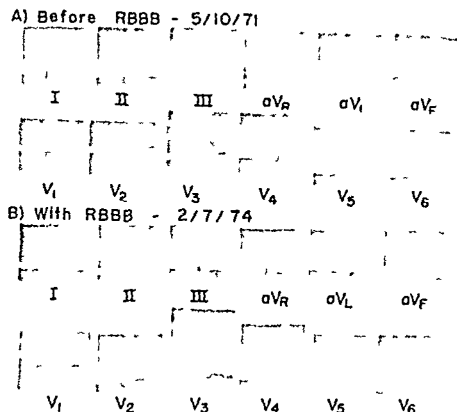


Fig 8 Serial electrocardiograms of a 76 year old man before and after he developed right bundle branch block

with an increase in the AP diameter of the chest, lowering of the diaphragm, and kyphoscoliosis

Bundle branch block (BBB) is encountered frequently in old people (Fig 8) It is found in 8 per cent of people 70 years of age or older[24] In a study of 1 160 patients over 60 years of age[25] 37 per cent had complete BBB 19 with left BBB and 38 with right BBB These conduction defects are not necessarily associated with hypertension hypercholesterolemia CHF, or a large heart

Eight per cent of 2 310 elderly patients had atrial fibrillation[24] The prognosis of patients with atrial fibrillation is determined by the total clinical data and not by the arrhythmia alone Premature contractions are the most frequent disturbances in cardiac rhythm in old patients Again, the significance depends upon all clinical data Premature contractions are more common in patients with organic heart disease Because of the lack of adequate data in old people the importance incidence, and management of such arrhythmias and the prognosis remain unknown All normal configurations and abnormalities of the ECG encountered in young people may be encountered in old people

The spatial vectorcardiogram (sVCG) has been studied very little in elderly people Spatial vectorcardiography is a sensitive method because of the nature of the recording as indicated previously[26] The sVCG recorded with the equilateral tetrahedral reference system reveals rather *characteristic distortion of the QRS sÊ loop in old people (Fig 6)*[26] *Even the QRS sÊ loops of 'normal'* old people are greatly distorted a readily noted difference from the smooth and regular QRS sÊ loop of normal young people These changes are detected more effectively with the equilateral tetrahedral reference system than with the Frank system of electrode placement[27]

Common cardiac diseases of old people

Seventy two per cent of all cardiovascular *deaths in the United States occur after the age of* 65[2] Although the most common cardiac disease among the aged is ischemic heart disease, almost all diseases of the heart in young patients may be found in old patients It is not possible to discuss in detail all of the cardiologic problems and diseases that may be found in geriatric patients *Nevertheless* it may be interesting to discuss in a general way some of the cardiologic problems and diseases of common occurrence in old patients A few of these are therefore discussed below

Ischemic heart disease increases in incidence with age to reach almost 100 per cent among pa

tients over 70 years of age [2] About one fourth of those who die of myocardial infarction do not have coronary thrombosis as the cause Biorck[28] found the mortality from myocardial infarction to be high in old patients being about 33 per cent for the 60 to 69 year age group 47 per cent for the 70 to 79 year age group and 64 per cent for patients 80 years of age or older Furthermore only one out of four patients will survive their infarction if they live beyond the first day Although silent infarctions are frequent in old people they carry a better prognosis than those associated with pain and discomfort Systolic blood pressures of less than 100 mm Hg and more than 200 mm Hg during myocardial infarction are serious signs. About 45 per cent of old people with myocardial infarction die of their myocardial infarct before they reach the hospital Seventy five per cent of patients with ventricular aneurysm develop intractable CHF with with 75 per cent of them dying within five years [2]

Cor pulmonale develops with old age in response to kyphosis emphysema loss of elastic tissue pulmonary fibrosis chronic bronchitis pulmonary infarctions previous infections and exposure to occupational dusts irritants and chemicals. All of these produce pulmonary hypertension anoxia anoxemia and disturbances in respiratory reflexes (Hering Breuer reflexes) Acute or chronic pulmonary embolism may produce acute and chronic cor pulmonale These latter states may remain undetected unless the physician keeps the problem in mind and studies the patient for the disease Too frequently they are not recognized until postmortem examination

It is estimated that 9 per cent of old patients with CHF have cor pulmonale and 2 per cent without CHF have it [7] Pulmonary embolism is extremely common in old people reaching 30 per cent in the eighth decade and 41 per cent in the ninth decade [11] Fractures obesity varicose veins hemiplegia and congestive heart failure are among the causes Pulmonary embolism is usually difficult to recognize in elderly patients. Tachycardia with right or left ventricular CHF often suggests the diagnosis Pleuritis is not common A mucoid sputum containing blood is extremely important diagnostically Massive pulmonary emboli precipitate circulatory collapse The diagnosis is suggested by the tachycardia atrial fibrillation unresponsive to digitalis, increased venous pressure right ventricular gallop

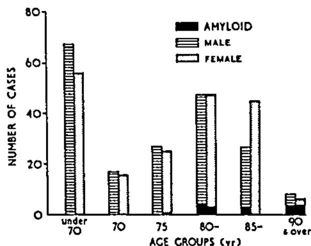


Fig 9 Incidence of cardiac amyloidosis in patients according to age and sex (From Pomerance A Senile cardiac amyloidosis Br Heart J 27 711 1965)

rhythm roentgenographic evidence of a pulmonary parenchymal lesion calf tenderness and edema of the involved leg with warmth and dilation of the superficial veins of the leg Furthermore a patient with heart disease especially CHF who suddenly deteriorates may have pulmonary embolism as the cause The ECG often is helpful with T wave inversion in Leads V_3 and V_4 and an $S_1 Q_3 T_3$ pattern in the limb leads P pulmonale complexes would certainly suggest pulmonary embolism

Chronic pulmonary heart disease is an ever increasingly important problem in old people Such patients usually have had a productive cough with wheezing for many years with winter colds They usually are smokers exposed to respiratory irritants of many sorts The clinical study will reveal the chronic pulmonary disease with x ray evidence of a dilated pulmonary conus and main pulmonary arteries and right ventricular enlargement The degree of pulmonary disease is usually moderate to severe with central cyanosis and blood gas studies that reflect poor blood aeration Depending upon the severity of the disease clubbing of fingertips and other signs of chronic pulmonary disease are intermingled with the signs of right ventricular disease with or without CHF

Cor pulmonale should be considered in all elderly sick patients It may vary from a mild disease to a severe and incapacitating illness It is common in old people

Senile amyloidosis of the myocardium is common in old people Amyloid depositions in the

heart, known since 1876, are too frequently unknown to physicians, even to cardiologists, as a degenerative change of old age It has been found in 10 per cent of patients between 80 and 90 years of age and in up to 50 per cent of patients dying at 90 years of age and older (Fig 9)[29] These focal deposits of amyloid increase in incidence with age Also the older the patients the greater the amount of amyloid accumulation There is a tendency for the amyloid to gather in subendocardial areas of the left atrium The amyloid depositions are readily overlooked on routine gross and microscopic study

There is no statistically significant sex difference in incidence There is a tendency for a greater incidence in males however There is no relationship of the severity of amyloidosis to heart weight As would be expected there are no characteristic clinical or ECG manifestations of senile myocardial amyloidosis Congo Red and other such diagnostic methods are not helpful since the amyloid is confined almost entirely to the heart There is no organ to biopsy except the heart and this is not indicated in old people Plasma protein electrophoresis may help in diagnosis The albumin fraction is decreased and the α_2 and γ globulins are increased These changes are not specific

Amyloid depositions in the heart result in myocardial failure and an increased sensitivity to digitalis Treatment is directed at the congestive heart failure

Hypertensive heart disease The normal level of blood pressure in old people is not generally established or accepted Some clinicians will consider even 210/110 as normal values for old people[1] This is unreasonable The upper limit should be 150/90 or 160/100 The management of hypertension above 150/90 should vary with the individual patient Systolic hypertension secondary to the rigid arterial system due to arteriosclerosis offers considerable therapeutic difficulties in some patients High pressure in arteries will certainly predispose to the rupture of cerebral arteries to produce a stroke Therefore low normal levels of arterial blood pressure are preferable Malignant hypertension with papilledema hemorrhage and exudates of hypertensive retinopathy and hypertensive encephalopathy are extremely rare in old people Headaches giddiness, and vertigo are rarely due to hypertension in old patients, whereas hypertension tends to produce angina pectoris myocardial infarction, cardiomegaly and CHF in elderly patients The associated arteriosclerosis is an important contributing factor to heart disease in the geriatric patient.

The left ventricular enlargement, CHF, ECG changes left atrial, and left ventricular gallop rhythm are readily detected in the hypertensive patient The hypertension and CHF are treated in conventional fashion with careful consideration of the greater sensitivity of the old patient to all drugs especially digitalis and particularly when the patient has been on a low salt diet and thiazide diuretics

Finally, although benign essential hypertension and arteriosclerotic hypertension are the hypertensive diseases of old people the psychogenic component of the hypertension is extremely important Psychic stress and emotional disturbances in old patients can produce marked elevations in arterial blood pressure Old people react to physical and psychic stress just as young people do Sudden elevations in blood pressure can result in a stroke Undue physical exertion can suddenly increase blood pressure and produce fatal cardiovascular disturbances It is because of these reactions that patients with hypertension should rely on home recordings[30] of their blood pressure to regulate therapy and to learn what factors elevate their pressure and what factors predispose to a low or normal pressure The patient can avoid the former factors and favor the latter[31]

Rheumatic heart disease is fairly common in elderly patients The diagnosis is often missed Its incidence in the aged is about 4 per cent[11] Bedford and Caird[32] studied 126 patients over 65 years of age carefully for heart disease in England and found 40 per cent of their patients with rheumatic heart disease to have had a history of rheumatic fever This percentage would be considered relatively high today in the United States About one half of their elderly patients with rheumatic heart disease had predominantly aortic valve stenosis with incompetence Two thirds of these patients had aortic valve disease with incompetence alone and 15 per cent of these patients had pure stenosis Atrial fibrillation with CHF occurred in many of these patients

Mitral valve disease with stenosis and the associated manifestations occurs in the elderly patient with rheumatic heart disease The ECG and

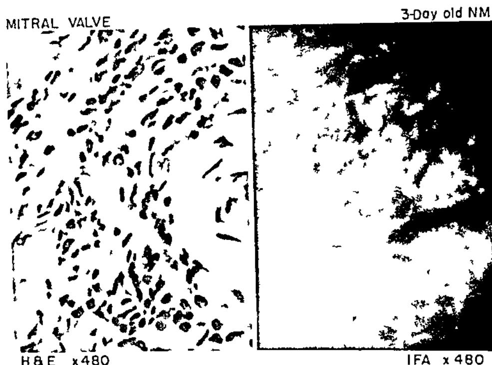


Fig 10 Sections of mitral valve from a three day-old infant showing inflammation with cellular infiltration and proliferation (left) and positive indirect immunofluorescent antibody staining (right) for Coxsackievirus B_4 ×480 (From Burch G E Sun S C Colcolough H L Sohal R S and DePasquale N P Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques AM HEART J 74 13 1967)

x ray manifestations are essentially the same as those in young patients however Kerley s lines are not common and signs of pulmonary hypertension due to the disease are rare

Papillary muscle dysfunction[33] commonly develops with old age This is not usually due to rheumatic valvular disease or streptococcal damage but rather it is generally due to the associated ischemic disease of the papillary muscles with scarring and other varying morphologic and functional myocardial damage due to impairment of blood supply to the terminal areas of the ventricular myocardium, the papillary muscles. Viral myocarditis however with resultant damage and later scarring of the papillary muscles may be another factor or at least a contributing etiologic factor The degree of hemodynamic disturbance that follows varies from slight to severe

Prognosis of rheumatic heart disease in elderly patients tend to be good however in patients who also have mitral stenosis and atrial fibrillation 20 per cent may develop systemic embolism[11]

Difficulties in differential diagnosis occur in patients who seek medical care for the first time in old age When followed for their rheumatic heart disease from their youth the diagnosis is readily established. Old people tend to develop calcific disease of the aortic and mitral valves in old age independent of previous valve injury by rheumatic fever Therefore these lesions are too frequently and erroneously considered to be of rheumatic fever origin

Viral heart disease is seldom given consideration in the aged Nevertheless viruses are known to produce heart disease and some viruses particularly the picornaviruses are highly cardiotropic for man Viruses can cause acute and chronic myocarditis valvulitis mural endocarditis coronary arteritis and pericarditis[34 37] In fact, the lesions of the valves (Fig 10) and myocardium (Fig 11) produced by viral infections are essentially indistinguishable from those attributed to rheumatic heart disease considered to be caused by the streptococcus[36] However many patients with such lesions have never had a history of rheumatic fever or documented

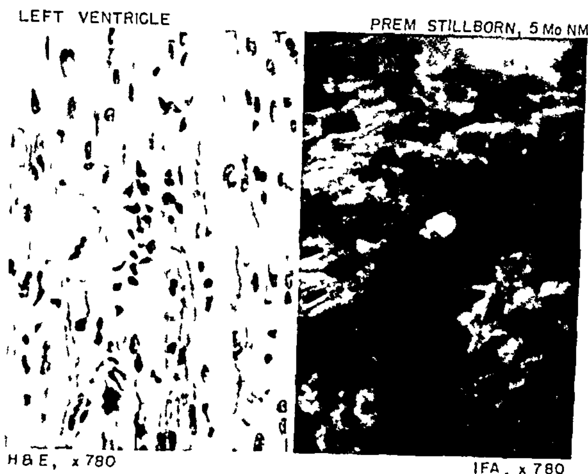


Fig 11 Sections of left ventricular *myocardium from a premature stillborn baby showing necrosis of muscle* fibers (left) and positive indirect immunofluorescent antibody staining for Coxsackie virus B_3 (right) ×780 (From Burch *G E Sun S C Chu K C Sohal R S* and Colcolough *H L* Interstitial and Coxsackievirus B myocarditis in infants and children JAMA 203 1 1968)

streptococcal infection with cardiac injury It is highly likely that the heart lesions in many of these patients were produced by viruses rather than by the streptococcus It is also possible that the streptococcus as well as other factors acts as a conditioning agent for latent or slow viruses which may remain dormant in the heart until stimulated by viral or bacterial infections or stress of any sort This may be comparable to the situation for herpes labialis due to the herpes simplex virus Certainly mixed viral and bacterial infections are not uncommon The lack of viral diagnostic laboratories in most general hospitals makes it difficult to determine the role of viruses in the production of heart disease in clinical medicine Nevertheless viruses must be considered among the important etiologic factors for acute and chronic heart disease among people of all age levels including old people The lesions found in the hearts of old patients due to infections in early life are the tombstones or scars or chronic healed lesions of previous acute infections [38] This probably applies in part at least to arteriosclerosis[38] and renal disease as well [39]

Aortic stenosis is fairly common in old age The aortic ejection murmur heard so frequently in old patients may be due to calcific aortic valve disease to dilation of the root of the aorta or to an arteriosclerotic plaque which protrudes into the lumen of the aorta to produce turbulence in blood flow Two thirds of patients over 70 years of age *have an aortic systolic ejection murmur due* at least to thickened aortic cusps [11] Heavy calcification is found in many of these aortic valves *Aortic sclerosis or thickened valves due to fibrosis* should be distinguished from calcific aortic stenosis Many of the aortic stenotic lesions are attributed to congenital bicuspid valves with degeneration This is often an erroneous opinion *A congenital lesion is often difficult to identify in* severely sclerotic and calcified valves

Aortic stenosis is often asymptomatic and *often difficult to detect in old patients with CHF* and feeble left ventricular contractions However, about 40 per cent of the patients with aortic stenosis have dyspnea angina pectoris or syncopal attacks The associated murmur is usually characteristically *loud and harsh but is often*

faint and short The ECG recordings show evidence of left ventricular hypertrophy (LVH) and the x ray studies with tomograms reveal not only the LVH but also the calcified valve

Aortic insufficiency is usually associated to some degree with calcific or sclerotic aortic valve disease The most common causes are rheumatic valvulitis calcific disease of old age and functional arteriosclerotic aortic disease Aortic insufficiency in elderly patients may also be due to ruptured cusps bacterial endocarditis dissecting aneurysm and aortitis associated with spondylitis It is rarely due to luetic heart disease in the United States anymore Dilation of the root of the aorta of old patients may cause aortic valve incompetence but it rarely produces sufficient pressure or volume leaks to cause clinically significant hemodynamic disturbances.

Thyroid heart disease due to hyperthyroidism or myxedema is of sufficient frequency in old patients to require constant consideration Occult or masked hyperthyroidism occurs fairly frequently in old people rendering the diagnosis of hyperthyroidism difficult to recognize clinically at times However with laboratory methods available at present the diagnosis is easy to establish if thyroid disease is considered by the physician Early recognition is imperative in old people since thyroid heart disease is reversible and curable when treated early

Other types of heart disease There are many other types of heart disease to be found in old people even congenital defects Congenital defects are present only if the defects are mild or produce little disturbances in cardiac function so that people can live to old age in spite of them Once ischemic heart disease the most common of all heart diseases in old people has been eliminated, the other cardiac diseases and lesions should be carefully considered The least common ones are not discussed

General remarks

The fundamental problem related to gerontology including geriatric cardiology is the phenomenon of the aging process itself There is a need to learn more about the process of aging with the hope of modifying or controlling aging as exemplified by the juvenile hormone in insects [40 41] Surely a definite effort should be made to learn more about the aging process in an effort not only to control but also to delay aging which in turn would postpone in any person s lifetime the chronologic period at which geriatric cardiology and the associated gerontologic states would become problems It is not inconceivable that an agent could be found which would delay aging or even maintain a status quo in a man s lifetime so that the aging process would suddenly become essentially arrested for some time Furthermore there is a need to know the factors and mechanisms responsible for senescence Such investigations should receive extensive support from all agencies institutions and scientists

Summary

Geriatric cardiology requires special knowledge and experience It is not possible to extrapolate directly experience obtained with young patients to old people Because of the multiple illnesses many serious in the elderly cardiac patients it is imperative for the cardiologist to be first of all a master internist *at all times* Old patients with their multiple illnesses are also sensitive to drugs including digitalis and diuretics There is a need to train more physicians in geriatric cardiology in order to offer the old patient the best of care since so many old people are living today There is also a need to learn the effects of the aging process itself on the human heart. Such studies should command priorities in financial and other forms of support

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Electrophysiology and pharmacology of cardiac arrhythmias III The causes and treatment of cardiac arrhythmias Part A*

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There are several approaches to the prevention and treatment of cardiac arrhythmias If an abnormality of rhythm clearly results from operation of a mechanism extrinsic to the heart treatment can be directed toward that mechanism A familiar example illustrating this is provided by the patient with hyperthyroidism If an arrhythmia clearly results from a drug acting on a heart which is not intrinsically arrhythmic usually it is sufficient to reduce the dose of drug or eliminate it entirely Perhaps the best known example of iatrogenic arrhythmia is digitalis intoxication Other arrhythmias can be prevented and treated by interventions which do not modify the electrical activity of the heart as their primary action For example arrhythmias resulting from congestive heart failure often can be eliminated by improving cardiac compensation those resulting from abnormalities of ventilation and acid base balance can be suppressed by appropriate control of PO_2 and pH and those caused by inadequate myocardial perfusion often can be reduced by decreasing the requirement for coronary blood flow

In addition to these indirect approaches to the prevention and control of arrhythmias often it is necessary to employ a therapeutic intervention which directly influences the electrical activity of the heart or some part of it Here there are three general classes of interventions the use of electrical stimulation surgical intervention and the use of pharmacologic agents We are concerned with the third the use of pharmacologic agents When it has been established that a disturbance of rhythm or conduction requires treatment and that the benefits to be derived from treatment outweigh the risk of treatment it might seem that the choice of drug would be fairly straightforward. Unfortunately often this is not the case Selection of an appropriate antiarrhythmic agent often requires and ideally always should require a correct and precise identification of the nature and cause of the arrhythmia Selection also should depend on an understanding of all the effects of the drug to be employed and not just its reported action against the arrhythmia under consideration There are three major reasons for these assertions Pharmacologic agents often have different effects on different cardiac tissues for example the use of a β adrenergic blocking agent such as propranolol to slow sinus rate may cause atrioventricular conduction block Many drugs used to modify cardiac rate and rhythm have both direct and indirect effects on the heart quinidine usually will decrease the rate of impulse initiation in atrial tachyarrhythmias but because of this effect simultaneously may increase the number of impulses which propagate to the ventricles Finally the response of the heart to a pharmacologic agent often is dependent on the physiologic state

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Drs Rosen d Wit e Se o In est g tors of the N w York Hea t Assoc tion.

Table I *Mechanisms for cardiac arrhythmias*

I Abnormal automaticity	*II Abnormal conduction*	*III Coexisting abnormalities of automaticity and conduction*
A *Site of impulse initiation*	A *Causes of impaired conduction*	A *Phase 4 depolarization & impaired conduction*
1 Normal (sinoatrial node)	1 Partial depolarization	1 Specialized cardiac fibers
2 Abnormal	2 Incomplete repolarization	B *Abnormal automaticity & impaired conduction*
a Atrial specialized fibers	3 Reduced responsiveness	1 Specialized cardiac fibers
b A V junctional fibers	4 Anatomical discontinuity	a Afterdepolarizations
c His Purkinje fibers	5 Abnormal response	b Other
d Atrial fibers in A V valves	B *Slowing and block*	2 Other cardiac fibers
B *Normal automatic mechanism*	1 Sinoatrial block	C *Parasystole*
1 Abnormal Rate	2 Atrioventricular block	
a Tachycardia	3 His bundle block	
b Bradycardia	4 Bundle branch block	
2 Abnormal rhythm	5 Purkinje fiber block	
a Premature impulses	C *Unidirectional block & reentry*	
b Delayed impulses	1 Ordered reentry	
c Absent impulses	a Sinoatrial node and junction	
C *Abnormal automatic mechanisms*	b A V node and junction	
1 Afterdepolarizations	c His Purkinje system	
2 Incomplete repolarization	d Purkinje fiber muscle junction	
3 Other	e Abnormal A V connections (WPW)	
a Oscillatory depolarizations at low membrane potential	2 Random reentry	
b Other	a Atrial muscle	
	b Ventricular muscle	

of the heart Since drugs usually are employed to modify the performance of the diseased heart, this consideration is of paramount importance

Unfortunately often we do not know enough about either the causes of abnormal cardiac rhythm and conduction or the actions of antiarrhythmic agents on normal and diseased cardiac tissues to make a completely rational decision concerning antiarrhythmic therapy Nevertheless, in so far as possible the basis for decision should include (1) a precise diagnosis of the abnormality to be treated (2) an understanding of the electrophysiologic basis for the abnormality and (3) knowledge of the anticipated effect of the drug or drugs to be employed on both normal and abnormal cardiac cells In this section we will present a general scheme which embodies this approach in subsequent sections we will present available information about the actions of specific antiarrhythmic drugs

Mechanisms for cardiac arrhythmias

Some years ago we concluded that an understanding of the mechanism of action of antiarrhythmic agents required the understanding of the causes of arrhythmia [1] Also although recognizing the multitude of clinical and electrocardiographic diagnoses of arrhythmias and conduction disturbances we proposed a simple generalized classification of arrhythmias based on underlying mechanisms [2] The present form of this classification is shown in Table I To facilitate an understanding of the mechanism of antiarrhythmic action of drugs we have subdivided arrhythmias into three general classes I Those resulting from an abnormality of automaticity or impulse generation II Those resulting from an abnormality of impulse conduction III Those resulting from coexisting abnormalities of automaticity and conduction This highly simplified scheme perhaps deserves some amplification

Abnormal automaticity For the arrhythmias caused by abnormal automaticity it is clear that many result from a change in the normal automatic mechanism—i e slow diastolic or Phase 4 depolarization (Fig 1) Alterations in normal automaticity can result in changes in rate rhythm and site of origin of the impulse For example an increase in the slope of Phase 4 depolarization in cells of the sinoatrial node might result in a sinus tachycardia (I B 1 a) a decrease in the slope of Phase 4 in the same cells might result either in sinus bradycardia (I B 1 b) or in escape of an ectopic automatic site (I A 2 b) Escape of an ectopic automatic site also might occur if automaticity at that site were enhanced as by the action of cate

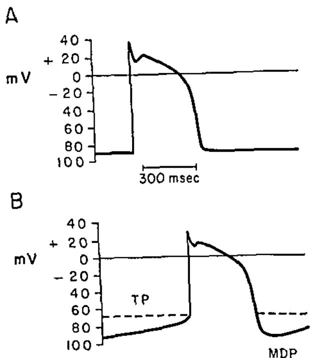


Fig 1 A and B Transmembrane action potentials of canine cardiac Purkinje fibers showing the steady transmembrane resting potential recorded from non automatic fibers *(A)* and the slow diastolic (Phase 4) depolarization characteristics of automatic fibers *B*. The ordinates show transmembrane potential in millivolts the abscissae time in milliseconds *TP* identifies the voltage level of the threshold potential *MDP* refers to maximum diastolic potential.

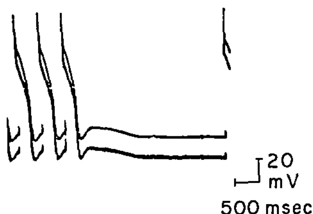


Fig 2 Transmembrane action potentials recorded from a canine cardiac Purkinje fiber poisoned by an excessive concentration of ouabain Note that each repolarization is followed by Phase 4 depolarization When the drive stimulus is discontinued (after the third cycle) both fibers have delayed afterdepolarizations which fail to attain threshold potential and thus do not initiate action potentials Electrical quiescence then persists until the drive stimulus is reinstituted (Rosen M and Merker C)

cholamines so as to cause either premature atrial depolarizations or an ectopic atrial rhythm In general for this part of the classification changes in rate or rhythm are assumed to result from (a) enhancement or depression of automaticity in the normal pacemaker or (b) enhancement of automaticity of an ectopic or latent pacemaker The latter may be located in any one of the specialized cardiac fibers or tissues For one of these abnormal sites the atrial fibers in the A V valves (I A 2 d) evidence for participation in atrial arrhythmias in humans is not yet available [3]

It is likely that mechanisms other than the normal one can cause automatic firing of cardiac fibers For example under certain conditions specialized fibers in the atria and ventricles of mammalian hearts develop afterdepolarizations (I C 1) These also have been called low amplitude potentials (LAP)[4] and transient depolarizations (TD)[5] (Fig 2) Afterdepolarizations respond to changes in rate and rhythm in a manner opposite to the normal automatic mechanism in that they increase in amplitude when the preceding cycle is shortened or when rate increases If their amplitude is sufficient they may attain threshold potential and initiate one or more action potentials This mechanism can operate in atrial tissues from human hearts[6] and presumably in human specialized ventricular fibers as well A frequent cause of delayed afterdepolarizations is the action of excessive concentrations of digitalis[4,5] and it is possible that this mechanism is responsible for some of the atrial junctional and ventricular rhythms recorded from humans intoxicated by digitalis as well as for the phenomenon of repetitive ventricular response [7,8]

The other abnormal mechanisms for automatic firing listed in Table I are not intended to include all possibilities but merely to represent several which have been demonstrated repeatedly in experiments on cardiac tissues from the hearts of laboratory animals and which probably should be considered in future studies on human hearts Incomplete repolarization (I C 2) may leave the membrane potential of some fibers so close to the threshold potential that repetitive firing occurs This change in electrical activity can be caused by a variety of pharmacologic agents and may also result from pathologic processes Oscillatory depolarizations at low levels of membrane potential (I C 3 a) have been produced

in cardiac Purkinje fibers by a variety of means including the action of excessive concentrations of catecholamines[9] Whether or not this mechanism causes arrhythmias of the human heart is not known at present

Abnormal conduction The arrhythmias caused by abnormalities of conduction probably are much more frequent than those resulting from abnormal automaticity The first major class here includes disturbances of rhythm caused by slowing or block of impulse propagation (II B) The causes of such impairment of impulse propagation are many and only major examples are listed (II A 1 5) In general propagation of the impulse may slow or fail because either (a) the impulse becomes insufficient to excite fibers along the path for propagation (b) excitability of fibers in advance of the propagating impulse is reduced or (c) because there is an actual interruption in the path as might result from loss of viable fibers The causes of a decrease in the stimulating efficacy of the propagating action potential include but are not limited to partial depolarization incomplete repolarization and replacement of the normal action potential by a slow response[10] Another change which can limit the ability of the action potential to propagate is a reduction in responsiveness this is a frequent effect of antiarrhythmic agents[11] The sorts of arrhythmias which are associated with depression or block of conduction include those which result from transient or continuing sinoatrial block which may be partial or complete (II,B 1) atrioventricular block (II B 2) or block in the His bundle the bundle branches and perhaps at the junction of peripheral Purkinje fibers with ventricular muscle

A special case of abnormal conduction is the condition in which there is unidirectional block and re entry (II C) The causes of this condition are similar to those which have been described in the preceding paragraph The unique aspect of unidirectional block is that when it is associated with sufficient slowing of conduction re entry or re excitation of the heart can occur[10] If the unidirectional block and associated re entry have a single and presumably fixed anatomical locus the condition can result in a variety of well known arrhythmias including re entrant atrioventricular junctional tachycardias and ventricular tachycardia If the sites of block and re entry vary in a random manner then atrial or ventricular fibrillation will be present

Coexisting abnormalities of automaticity and conduction The final category of arrhythmias is perhaps somewhat artificial but is included to emphasize the frequent association of altered automaticity and abnormal conduction and of abnormal conduction and ectopic automatic firing Phase 4 depolarization reduces the transmembrane potential and a reduction in transmembrane potential will diminish the ability of a fiber to generate a normal action potential[12] Thus if Phase 4 depolarization is enhanced in some part of the specialized conducting system or if Phase 4 depolarization proceeds for an unusually long time the response to a propagating impulse often will be abnormal and conduction will be impaired This is the most likely cause of abnormalities in impulse propagation associated with long diastolic intervals[13]

The association between abnormalities of automaticity and conduction is particularly important in considering the phenomenon of parasystole (III C) If there were no abnormality of conduction (entrance block) the automatic parasystolic focus could not exist since each sinus impulse would depolarize the potentially automatic site If there were no abnormality of conduction (exit block), a rapid ectopic automatic focus would not establish a parasystolic rhythm since all impulses generated by the focus would excite the heart or at least the atria or ventricles The possible association between abnormal automatic mechanisms and impaired impulse propagation (III B) has been explored only for afterdepolarizations[4,14] This type of partial depolarization like normal Phase 4 depolarization impairs propagation by reducing membrane potential and may cause local delay of excitation and re entrant excitation

Treatment of arrhythmias

Abnormal automaticity The rate at which a normally automatic cell or fiber group generates impulses is controlled most strongly by three variables (a) the slope of Phase 4 depolarization (b) the value of the threshold potential and (c) the value of maximum diastolic potential (Fig 3) Pharmacologic manipulation of any one, or of several of these variables should in theory permit control of arrhythmias resulting from a dis

turbance of the normal automatic mechanism For example if the sinoatrial pacemaker generates impulses at an abnormally rapid rate either intensification of the effects of the vagus or attenuation of the effects of the sympathetic nerves will decrease the slope of Phase 4 depolarization and cause sinus slowing Many of the antiarrhythmic drugs can in sufficient concentration exert similar effects However there are serious limitations to this exhibition of antiarrhythmics which will be described in subsequent sections

If an ectopic automatic focus partially or completely controls the cardiac rhythm because the sinus rate is abnormally slow or because the sinus rhythm is abnormally irregular restoration of normal cardiac rhythm can be effected by increasing or regularizing the sinus rhythm This type of abnormality can be treated with agents which enhance the automaticity of the sinus pacemaker such as atropine or catecholamines Both act primarily by increasing the slope of Phase 4 depolarization Unfortunately if depression of sinus automaticity is due to disease as in the sick sinus syndrome [15] often it is impossible to enhance impulse generation to a satisfactory extent Also since all normally automatic supraventricular pacemakers are sensitive to atropine and catecholamines and all normally automatic cells are sensitive to catecholamines, restoration of sinus rhythm often depends on a relatively greater sensitivity of the sinoatrial fibers to the agent employed One could also depress automaticity of ectopic pacemakers with antiarrhythmic drugs and thus permit the sinus to resume dominance but clearly there may be problems associated with this approach Restoration of sinus rhythm once again depends on differential sensitivity of various groups of automatic fibers and even if a sinus pacemaker resumes dominance its rate may be insufficient

When arrhythmias are due to enhanced normal automaticity at an ectopic site treatment again can be directed towards increasing sinus rate and thus suppressing the ectopic focus In the latter case the standard antiarrhythmic drugs often are effective since in most instances they act more strongly on the subsidiary pacemakers than on the sinus node The major generalization to remember is that when any normally automatic focus is driven by propagating impulses at a rate greater than its intrinsic

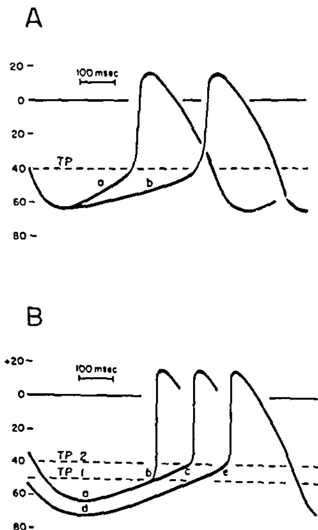


Fig 3 A and B Transmembrane action potentials typical of those recorded from fibers of the sinoatrial node showing the expected effects of changing the slope of Phase 4 depolarization the magnitude of the maximum diastolic potential and the level of the threshold potential In *A* when the slope of Phase 4 is decreased from *(a)* to *(b)* more time is required to reach threshold potential and the cycle length is increased In *B* under control conditions *(TP 1)* the fiber depolarizes from a maximum diastolic potential of *(a)* and attains threshold at *(b)* If threshold potential shifts to a less negative value *(TP 2)* the Phase 4 depolarization will not attain threshold until *(c)* If maximum diastolic potential is increased to *(d)* Phase 4 depolarization will not attain threshold until *(e)* Opposite changes in the slope of Phase 4 the value of TP or the value of MDP would have the opposite effect on cycle length and rate (Modified after Hoffman and Cranefield Electrophysiology of the Heart New York, 1960 McGraw Hill Book Company Inc Reproduced with permission)

rate, not only is it prevented from firing but also its automaticity is actually depressed This phenomenon of overdrive suppression[16,17] is important both in abolishing ectopic rhythms and in suppressing automatic premature depolarizations

Since the rate of a normally automatic focus is a function not only of the slope of Phase 4 depolarization but also of the values of the threshold potential and maximum diastolic potential (Fig 3) pharmacologic manipulation of the latter two variables should permit control of arrhythmias In practice however, control of the slope of Phase 4 is safest and most effective It is possible to shift the threshold potential towards zero and thus slow the rate of automatic firing Indeed, many antiarrhythmic drugs in sufficient concentration have this effect However, it should be remembered that the level of threshold potential is important not only in relation to the firing of an automatic focus but also in relation to propagation of the impulse throughout the heart. As threshold potential shifts to values closer to zero it is more difficult for the propagating impulse to excite and, when excitation occurs, the resulting action potential may show a reduced rate of rise and amplitude These effects, in concert tend to slow conduction and increase the likelihood of block A decrease in maximum diastolic potential might be expected to increase rate but also would depress responses

It is possible also to increase the maximum diastolic potential of an automatic fiber and thus slow the rate at which it will fire Acetylcholine by increasing permeability of the membrane to potassium has this effect on all normally automatic supraventricular fibers Some antiarrhythmic drugs such as lidocaine[11] have a similar effect on fibers of the His Purkinje system Finally, at times the transmembrane potential of a fiber group may be depressed because the transmembrane ionic concentration gradients are abnormal Under such conditions either improved perfusion of the extracellular space or enhancement of active transport of ions across the membrane may increase membrane potential There is some evidence that catecholamines can improve active transport[17] and in this manner influence the automaticity of cardiac Purkinje fibers and also cells in atrial parasystolic foci [18]

The automaticity of specialized cardiac fibers is strongly influenced by the environment and condition of the fiber Elevations of extracellular calcium ion concentration shift threshold potential towards zero and may depress automaticity and a low calcium concentration has the opposite effect A high extracellular potassium concentration decreases both maximum diastolic potential and the slope of Phase 4 depolarization while low potassium, within limits has the opposite effect. The therapeutic importance of these effects is limited, however, and except in the case of automaticity which has been enhanced by digitalis manipulation of the extracellular ionic environment often does not cause predictable changes in rate and rhythm Automaticity also is influenced by the general condition of cardiac fibers, for example, stretch and hypoxia tend to increase automaticity and relief of these problems can contribute to restoration of normal rhythm

One other special case of enhanced normal automaticity should be considered even though it has not yet been proved to have clinical importance All the fibers of the cardiac syncytium are connected internally so that whenever there is a difference in transmembrane potential between two adjacent groups of fibers current flows between them Parenthetically it is this arrangement which permits propagation of the impulse Because of this relationship if cells adjacent to a normally automatic fiber group are partially depolarized as by local ischemia, current will flow across the membrane of the automatic fibers and increase slope of Phase 4 depolarization. This effect may cause the fibers to initiate an ectopic rhythm In theory improved perfusion of the partially depolarized fibers if it increases their membrane potential should be an effective intervention

When an arrhythmia is caused by an abnormal automatic mechanism drug treatment should follow the same rules as when the normal automatic mechanism is the cause Alteration in the rate of rhythm of the normal sinus pacemaker may provide a mechanism for control This would be the case when ectopic impulses are due to afterdepolarizations However, in contrast to the case of the normal automatic mechanism, a decrease in rate can be expected to decrease the likelihood that afterdepolarizations will attain threshold and initiate ectopic impulses If pharmacologic agents are employed to suppress delayed afterdepolarizations some special rules

may have to be observed. It is true that acetylcholine can abolish this mechanism in atrial specialized fibers at least when it is caused by digitalis [19] and in this sense there is a similarity between the abnormal and normal automatic mechanisms However the drug sensitivity of this mechanism in Purkinje fibers may be different from that resulting from Phase 4 depolarization For example verapamil appears to be quite effective in suppressing Purkinje fiber after depolarizations which are caused by digitalis excess [20]

Abnormal conduction Pharmacologic treatment of conduction abnormalities can at least in some instances be considered in relation to the causes of the conduction abnormalities As has been described for automatic rhythms treatment may influence the problem either indirectly or directly If impaired or blocked conduction results from impulses encountering refractory tissues changing cardiac rate or rhythm may be sufficient to improve conduction Perhaps the best known example of this is the block of rapid or premature impulses in the A V node With a rapid atrial rate there may be partial or complete A V block with or without ventricular escape Abnormalities of rhythm can cause other problems With properly timed premature impulses there may be unidirectional block and slow conduction in the vicinity of the sinus node in the A V node within the His Purkinje system or at the junction of Purkinje fibers with ventricular muscle fibers If the conditions are appropriate [10] re entrant excitation will result If any of the cardiac tissues are modified or depressed by disease or drugs the likelihood of re entrant arrhythmia is enhanced. This suggests that control of rate and rhythm often may be sufficient to prevent abnormalities of rhythm which are due to impaired conduction

Since the level of membrane potential is an important determinant of the ability of a fiber to generate a normal impulse because there is increasing evidence that partially depolarized fibers often generate abnormal slow responses[10] and since slow responses propagate slowly and are particularly prone to undergo one way block and cause re entrant excitation it would seem that restoration or maintenance of a normal transmembrane resting potential would be important in preventing or abolishing many arrhythmias That this is the case can be demonstrated in experiments on isolated preparations of cardiac tissues In relation to therapeutic interventions however the range of possibilities is somewhat limited Poor perfusion and stretch can cause partial depolarization and sometimes there are means to improve perfusion or decrease the requirement for perfusion and decrease chamber volume Excessively rapid or premature stimulation which does not permit complete recovery can cause partial depolarization This effect is perhaps best demonstrated by the example of repetitive concealed conduction in the A V node Once again control of rate and rhythm can be an effective intervention Finally, at times there are means by which membrane potential can be increased through a direct effect of a pharmacologic agent Unfortunately in relation to arrhythmias caused by impaired conduction the number of useful agents is limited Catecholamines may increase resting potential of some partially depolarized fibers for humans this seems to be true at least in the case of diseased atrial fibers [21] There is evidence also for canine cardiac Purkinje fibers that diphenylhydantoin can increase the resting potential when it is moderately reduced [22] Other antiarrhythmic drugs probably do not share this effect. Finally it may be possible to improve the response generated by a depressed or partially depolarized fiber Again experimental data suggest that only diphenylhydantoin may act in this manner

Because our ability to improve conduction in *depressed fibers* is at present, so severely limited, most antiarrhythmic drugs are employed to further depress conduction in areas where reentry occurs This effect is exerted by all of the standard antiarrhythmic drugs and probably is the primary mechanism by which they prevent and suppress reentrant rhythms At times it is important that depressant drugs exert a more intense effect on some cardiac tissues than on others It is usual to assume that this is the case when reentrant rhythms occur in depressed fibers Also it is hoped that selective depression may occur when an anomalous A V pathway permits a reentrant tachycardia

Abnormal automaticity and conduction When abnormalities of automaticity and conduction coexist there are only a few special points to remember If Phase 4 depolarization or delayed afterdepolarizations cause impaired conduction suppression of either type of diastolic depolariza

rate, not only is it prevented from firing but also its automaticity is actually depressed This phenomenon of overdrive suppression[16,17] is important both in abolishing ectopic rhythms and in suppressing automatic premature depolarizations

Since the rate of a normally automatic focus is a function not only of the slope of Phase 4 depolarization but also of the values of the threshold potential and maximum diastolic potential (Fig 3) pharmacologic manipulation of the latter two variables should permit control of arrhythmias In practice however, control of the slope of Phase 4 is safest and most effective It is possible to shift the threshold potential towards zero and thus slow the rate of automatic firing Indeed, many antiarrhythmic drugs in sufficient concentration have this effect However, it should be remembered that the level of threshold potential is important not only in relation to the firing of an automatic focus but also in relation to propagation of the impulse throughout the heart. As threshold potential shifts to values closer to zero it is more difficult for the propagating impulse to excite and when excitation occurs the resulting action potential may show a reduced rate of rise and amplitude These effects, in concert tend to slow conduction and increase the likelihood of block A decrease in maximum diastolic potential might be expected to increase rate but also would depress responses

It is possible also, to increase the maximum diastolic potential of an automatic fiber and thus slow the rate at which it will fire Acetylcholine by increasing permeability of the membrane to potassium, has this effect on all normally automatic supraventricular fibers Some antiarrhythmic drugs such as lidocaine[11] have a similar effect on fibers of the His Purkinje system Finally at times the transmembrane potential of a fiber group may be depressed because the transmembrane ionic concentration gradients are abnormal Under such conditions either improved perfusion of the extracellular space or enhancement of active transport of ions across the membrane may increase membrane potential There is some evidence that catecholamines can improve active transport[17] and in this manner influence the automaticity of cardiac Purkinje fibers and also cells in atrial parasystolic foci[18]

The automaticity of specialized cardiac fibers is strongly influenced by the environment and condition of the fiber Elevations of extracellular calcium ion concentration shift threshold potential towards zero and may depress automaticity and a low calcium concentration has the opposite effect A high extracellular potassium concentration decreases both maximum diastolic potential and the slope of Phase 4 depolarization while low potassium, within limits has the opposite effect. The therapeutic importance of these effects is limited, however, and except in the case of automaticity which has been enhanced by digitalis, manipulation of the extracellular ionic environment often does not cause predictable changes in rate and rhythm Automaticity also is influenced by the general condition of cardiac fibers for example stretch and hypoxia tend to increase automaticity and relief of these problems can contribute to restoration of normal rhythm

One other special case of enhanced normal automaticity should be considered even though it has not yet been proved to have clinical importance All the fibers of the cardiac syncytium are connected internally so that, whenever there is a difference in transmembrane potential between two adjacent groups of fibers current flows between them Parenthetically, it is this arrangement which permits propagation of the impulse Because of this relationship, if cells adjacent to a normally automatic fiber group are partially depolarized as by local ischemia, current will flow across the membrane of the automatic fibers and increase slope of Phase 4 depolarization This effect may cause the fibers to initiate an ectopic rhythm In theory improved perfusion of the partially depolarized fibers, if it increases their membrane potential should be an effective intervention

When an arrhythmia is caused by an abnormal automatic mechanism drug treatment should follow the same rules as when the normal automatic mechanism is the cause Alteration in the rate of rhythm of the normal sinus pacemaker may provide a mechanism for control This would be the case when ectopic impulses are due to afterdepolarizations However in contrast to the case of the normal automatic mechanism, a decrease in rate can be expected to decrease the likelihood that afterdepolarizations will attain threshold and initiate ectopic impulses If pharmacologic agents are employed to suppress delayed afterdepolarizations some special rules

may have to be observed. It is true that acetylcholine can abolish this mechanism in atrial specialized fibers at least when it is caused by digitalis[19] and in this sense there is a similarity between the abnormal and normal automatic mechanisms. However the drug sensitivity of this mechanism in Purkinje fibers may be different from that resulting from Phase 4 depolarization. For example verapamil appears to be quite effective in suppressing Purkinje fiber afterdepolarizations which are caused by digitalis excess.[20]

Abnormal conduction Pharmacologic treatment of conduction abnormalities can at least in some instances be considered in relation to the causes of the conduction abnormalities. As has been described for automatic rhythms treatment may influence the problem either indirectly or directly. If impaired or blocked conduction results from impulses encountering refractory tissues changing cardiac rate or rhythm may be sufficient to improve conduction. Perhaps the best known example of this is the block of rapid or premature impulses in the A V node. With a rapid atrial rate there may be partial or complete A V block with or without ventricular escape. Abnormalities of rhythm can cause other problems. With properly timed premature impulses there may be unidirectional block and slow conduction in the vicinity of the sinus node in the A V node, within the His Purkinje system or at the junction of Purkinje fibers with ventricular muscle fibers. If the conditions are appropriate[10] re entrant excitation will result. If any of the cardiac tissues are modified or depressed by disease or drugs the likelihood of re entrant arrhythmia is enhanced. This suggests that control of rate and rhythm often may be sufficient to prevent abnormalities of rhythm which are due to impaired conduction.

Since the level of membrane potential is an important determinant of the ability of a fiber to generate a normal impulse because there is increasing evidence that partially depolarized fibers often generate abnormal slow responses[10] and since slow responses propagate slowly and are particularly prone to undergo one way block and cause re entrant excitation it would seem that restoration or maintenance of a normal transmembrane resting potential would be important in preventing or abolishing many arrhythmias. That this is the case can be demonstrated in experiments on isolated preparations of cardiac tissues. In relation to therapeutic interventions, however the range of possibilities is somewhat limited. Poor perfusion and stretch can cause partial depolarization and sometimes there are means to improve perfusion or decrease the requirement for perfusion and decrease chamber volume. Excessively rapid or premature stimulation which does not permit complete recovery can cause partial depolarization. This effect is perhaps best demonstrated by the example of repetitive concealed conduction in the A V node. Once again control of rate and rhythm can be an effective intervention. Finally at times there are means by which membrane potential can be increased through a direct effect of a pharmacologic agent. Unfortunately in relation to arrhythmias caused by impaired conduction, the number of useful agents is limited. Catecholamines may increase resting potential of some partially depolarized fibers for humans this seems to be true at least in the case of diseased atrial fibers.[21] There is evidence also for canine cardiac Purkinje fibers that diphenylhydantoin can increase the resting potential when it is moderately reduced.[22] Other antiarrhythmic drugs probably do not share this effect. Finally it may be possible to improve the response generated by a depressed or partially depolarized fiber. Again experimental data suggest that only diphenylhydantoin may act in this manner.

Because our ability to improve conduction in depressed fibers is at present so severely limited most antiarrhythmic drugs are employed to further depress conduction in areas where reentry occurs. This effect is exerted by all of the standard antiarrhythmic drugs and probably is the primary mechanism by which they prevent and suppress reentrant rhythms. At times it is important that depressant drugs exert a more intense effect on some cardiac tissues than on others. It is usual to assume that this is the case when reentrant rhythms occur in depressed fibers. Also it is hoped that selective depression may occur when an anomalous A V pathway permits a reentrant tachycardia.

Abnormal automaticity and conduction When abnormalities of automaticity and conduction coexist there are only a few special points to remember. If Phase 4 depolarization or delayed afterdepolarizations cause impaired conduction suppression of either type of diastolic depolariza

tion may be expected to improve impulse propagation Surprisingly, drugs which ordinarily impair conduction may cause improvement in this case For example low concentrations of procainamide, by decreasing the slope of Phase 4 depolarization in fibers of the His Purkinje system can actually improve conduction[23] In experiments on isolated preparations of cardiac Purkinje fibers, an appropriate elevation of extracellular potassium concentration has the same effect When digitalis has induced delayed afterdepolarizations in Purkinje fibers their abolition by verapamil can improve impulse propagation When a parasystolic focus is permitted to exist because impaired conduction results in entrance block an improvement in conduction can and will extinguish the parasystolic rhythm In theory, sufficient depression of conduction should result in complete exit block and thus isolate the parasystolic focus from the heart in practice the usual antiarrhythmic drugs often fail to have this effect

Annotations

The site of origin of venous thrombosis

It is possible that a greater knowledge of the natural history of venous thrombosis will give a clearer insight into its etiology Of special importance in this respect is the site of origin of the thrombus Opinions on this have undergone several changes since the time of Virchow when venous dissection was restricted to the proximal vessels of the thigh Such studies led Virchow in 1856 to conclude that venous thrombi originated in the ileofemoral segment

This view was maintained universally until about 1934 when clinicians such as Homans[1] Denecke[2] Olow[3] Ochsner[4] and Frykholm[5] observed that the clinical signs and symptoms of venous thrombosis originated in the calf and, with phlebographic support Bauer[6] concluded that this must be the most common site of origin

But later careful pathological studies[7 10] cast doubts on this concept and returned the origin of thrombus formation to the deep veins of the thigh. In McLaughlin and Paterson's[7] series of patients 73 per cent of the thrombi started in the thigh and pelvis Sevitt and Gallagher[8] established six sites along the length of the venous system at which thrombi originated, the incidence being only slightly higher in the calf than in the thigh. They established that thrombi often started at multiple sites and coalesced by proximal and distal extension.

Unfortunately pathological studies are necessarily performed on a highly selected group of patients and the results cannot be directly related to the clinical situation The development therefore of radioactive detection methods in the mid 1960's whereby the formation, progression, and resolution of the thrombus could be estimated in the living patient revolutionized the study of this condition

With the development of radioactive labeling of a thrombus emphasis has again been placed on the calf as the common site for thrombus formation Kakkar and colleagues,[11] using this technique showed that in surgical patients the majority of thrombi start in the calf veins and proximal extension occurs in only just over 20 per cent. Similar findings were reported in patients having medical treatment only for instance Maurer and co-workers[1] found 44 affected limbs in a series of 100 patients in a coronary care unit—41 were mid calf and three were lower calf in origin

In our own series of 100 consecutive surgical patients using conventional criteria[13] for the radioactive detection of thrombi the findings correspond with previous reports There was an over all incidence of 27 per cent with a distribution of thrombi throughout the limb as shown in Fig 1 with a predilection for the calf When, however the data were analyzed by the relative uptake method,[14] a different pattern emerged. First there was a greater total incidence of thrombosis. Of the 100 patients 69 had thrombi in a total of 118 affected limbs. The distribution of these thrombi is shown in the graph a pattern conforming closely to that found originally by Sevitt and Gallagher[8] the incidence being only slightly less in the thigh than in the calf We found

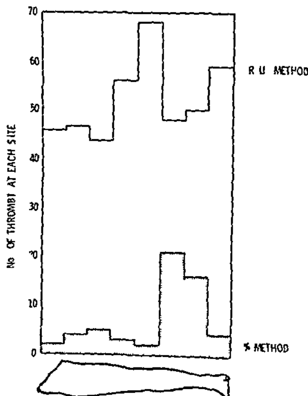


Fig 1 Distribution of venous thrombi

a peak incidence at the knee and ankle joints and in 62 of the limbs there was a single site of origin, in 49 limbs a double site and in seven limbs apparently three independent sites of origin. The presence of these thrombi was not confirmed by phlebography because we believe this would impose limitations on the sensitivity of the very method which it is designed to overcome In fact, the reliability of the method has been confirmed by observing the blood clearance of radioactive fibrinogen in these patients a complete correlation with the findings of the relative uptake method being obtained[15 16]

If we acknowledge the multifactorial etiology of venous thrombosis these findings must negate the relative importance of stasis in the process Indeed, the high incidence of thrombosis that we have detected raises the possibility that we are really *observing* a physiological process whereby small thrombi are continuously being formed and subsequently lysed. In only a minority of patients perhaps with a susceptible characteristic and under abnormal stresses such as surgery do these thrombi go on to form more extensive and pathological masses Unfortunately at present it is impossible to distinguish between the possibly physiological and

tion may be expected to improve impulse propagation Surprisingly, drugs which ordinarily impair conduction may cause improvement in this case For example, low concentrations of procainamide, by decreasing the slope of Phase 4 depolarization in fibers of the His Purkinje system can actually improve conduction [23] In experiments on isolated preparations of cardiac Purkinje fibers an appropriate elevation of extracellular potassium concentration has the same effect When digitalis has induced delayed afterdepolarizations in Purkinje fibers, their abolition by verapamil can improve impulse propagation When a parasystolic focus is permitted to exist because impaired conduction results in entrance block, an improvement in conduction can and will extinguish the parasystolic rhythm In theory, sufficient depression of conduction should result in complete exit block and thus isolate the parasystolic focus from the heart in practice the usual antiarrhythmic drugs often fail to have this effect

produced by stimulation is not satisfactorily worked out However it has been shown that following subarachnoid hemorrhage there is a denervation of the adrenergic fibers when attempts are made to stain them for as long as six weeks[14] The possible importance of this in terms of hyper sensitivity due to denervation and also the possible implica tions of the use of reserpine to reduce blood pressure in per sons with aneurysms and subarachnoid hemorrhage need consideration.

Turning to experimental subarachnoid hemorrhage sev eral authors maintain that acute spasm can be produced by the application of blood to vessels at the base of the brain in either acute or chronic animal preparations. This includes observations on dogs cats and monkeys[2 10 14 18] by micro scopic observations in acute or chronic models by demonstrating the changes in vessel siz by serial x ray angiography Fluorescein angiography has been used to dem onstrate changes in the epicerebral vessels in acute experi ments.[5] Our own experiments have produced evidence that local application of blood or platelet extracts on the basilar artery of cats can constrict the vessel Kapp and associates[10] have described this mod l in detail.

A chronic preparation u..ing macaque monkeys with an implanted reservoir[16 17] attached to a catheter in the basal cistern has convinced us that we have been able on repeated occasions to produce constriction of the basilar and suprachnoid carotids and anterior middle cerebral arteries as demonstrated by angiography In some instances repeat ing the examination in a week has shown evidence of per sistent chronic vasoconstriction

Investigators have studied vasomotor responses of pro staglandins Several authors have demonstrated that PGE_1 has a vasodilating effect but some have said that it is vasoconstrictive[2 15 19,20] Some confusion exists here because the substance has been dissolved in 5 per cent ethanol and the vehicle alone administered either intra arterially or in the cisterna magna has been found to be vasodilating[20] There is other evidence that PGF_2 alpha is vasoconstrictive[2] and we have found this also to be the case when applied to the basilar artery of the cat In fact it has been shown in our experiments to be extremely effective in some instances almost arresting blood flow in a segmental fashion This sub stance has been found to be present in platelets[9] It may be a possible explanation for the vasoconstriction after subarachnoid hemorrhage

Recognizing that the actual mechanism for the production of vasospasm remains in a large measure obscure treatment efforts have multiplied in an effort to relieve patients affected by this disastrous complication Papaverine at the time of operation appears to be transiently effective[11] Efforts using alpha blocking agents have gained some success[6] but this has not been significant in our experience and in well-established cases. Furthermore when as we believe the source of the problem is in the clotted blood closely applied to the artery that is involved, any pharmacologically competitive drug which is not able to be topically applied to the affected area and which must be tolerated by the body as a whole if it is to be given by any other route is immeasurably disadvantaged. Further if the vascular smooth muscle is to be relaxed or repolarized it must possess in its cells an adequate source of the chemical mechanism for relaxation or a rapid means for their production on stimulation. Thus it could be considered, for example that the dilating effect of papaverine which de pends on phosphodiesterase inhibition allowing cyclic AMP accumulation would be nonoperative if cyclic AMP could not be produced in adequate amounts Similarly alpha inhibi tors and beta stimulators may be rendered ineffective This leads to the investigation of supplying cyclic AMP ex ogenously[17] We have tried this in both acute and chronic ex periments and we have always observed dilatation following topical application Reports of different results with cerebral blood vessels have involved the intravascular administration. Control studies using normal saline did not produce dilatation When we have demonstrated that vessels have di lated under the influence of cyclic AMP they have remained so during the duration of the observation period even when they were stimulated mechanically or blood was applied or when subarachnoid hemorrhage was caused deliberately by tearing a small side branch near the vessel

One may argue that the drug is effective by way of stimulating the perivascular nerves and not by acting on the smooth muscle itself However since nerve stimulation is generally considered to be ineffective in altering vessel size this explanation is unlikely

We conclude that there may be a whole series of factors playing upon cerebral vascular smooth muscle probably subtly maintaining its tone and response to a variety of con ditions—blood pressure posture etc Under the unusual con ditions found in subarachnoid hemorrhage there arises a series of topical events often associated with segmental or more widespread vasoconstriction of cerebral blood vessels in the subarachnoid space It is felt that this involves in some way the intracellular activities of cyclic AMP its destruction by one or more substances which arise in the clot or in the formed elements of the blood. Experimentally the vasospasm is responsive to exogenously supplied cyclic AMP in the form of dibutyryl derivative either because cyclic AMP itself is unable to pass through the cell membrane or else because it is destroyed in transit. There is evidence that dibutyryl cyclic AMP is converted into cyclic AMP inside the cell

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so clinically irrelevant thrombus and the pathological and clinically very important thrombus

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Some considerations on cerebral vasospasm

Traditional views of cerebral blood vessels long held that they were not given to changes in caliber Also investigations of the alteration in cerebral blood flow following stimulation of cervical sympathetics have yielded inconclusive[8] results that would indicate that significant changes in vessel size did not in fact occur It has been held by many that only the small resistance vessels which respond to changes in the level of PCO_2 are really reactive [12] and that larger cerebral vessels do not show significant responses However there are other sources of evidence that would point to extreme reactivity on the part of cerebral blood vessels under various clinical conditions The most compelling is the vasospasm that follows subarachnoid hemorrhage usually about five to seven days after the event if it occurs at all [1,4,7] This is most often seen on angiography and it affects major vessels either segmentally or over a wider area of distribution [3] Since the small vessels which are thought to be the ones reactive to PCO_2 are beyond the resolution of x ray angiography this represents spasm in vessels which under other circumstances for example sympathetic stimulation are unresponsive For spasm to occur the vessel must be in the subarachnoid space Thus a sharp distinction may be made between the infra and supraclinoid portions of the internal carotid artery The vessel must also be in close contact with enmeshed subarachnoid blood clot This condition is not seen in association with intracerebral hematomas which are confined and do not involve the subarachnoid space and its associated major arteries

There may be acute spasm at the time of rupture of an aneurysm which may have faded by the time angiography has been attempted. The blood from hemorrhage remains and changes occur in the clot with beginning degeneration of the formed elements and lysis of the fibrin The degenerating blood which is closely applied to the vessel walls in the meshwork of subarachnoid trabeculae presents to them probably one or more mechanisms for excitation of smooth muscle cells either directly or by alteration in the nerve supply to the vessels either sympathetic or parasympathetic

Experimental evaluation of this problem has in a large sense been confined to two approaches First the investigation of the innervation of the cerebral blood vessels by demonstration of fluorescent catecholamines of the sympathetic fibers[13,14] or less directly by the method of demonstrating the presence of cholinergic nerve fibers [14] Experimental work done by Peerless and Kendal [14] for example has shown a gradual distribution of adrenergic fibers to the blood vessels of animals with the highest degree of innervation in the anterior part of the circle of Willis and with less innervation posteriorly as the basilar artery is approached This is thought to have some relevance to the serious problem of spasm associated with anterior communicating artery aneurysms. The balance of cholinergic and adrenergic effects

and aortic systolic pressures or the peak gradient We have validated this equation in ten patients with aortic valvular stenosis with peak gradients ranging from 15 to 110 mm Hg The comparison of the calculated mean Δ P from Equation 3 to that derived by manual planimetry was excellent (r = 0 97) with a standard error of ± 5 mm Hg

The utility of this simple calculation can best be appreciated in the cardiac catheterization laboratory where the severity of the stenotic aortic valve may be rapidly estimated from the peak systolic gradient Furthermore estimates of aortic valve area[2] which utilize the mean Δ P may be facilitated with this approach

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Of one mind

There is a tendency today to appoint committees to solve or dispose of problems This may be justified on certain democratic political or public relations principles but it will seldom get a good job done A committee of integrated minds is no stronger than its weakest mind and its most vociferous adamant and stubborn member To observe a committee function is an experience and a delusion " All members rarely prepare adequately for meetings A few members attempt to compensate for lack of preparation with much talking and activity during meetings — a compensation for their inferior knowledge and preparation Loud and constant talking or an aggressive behavior does not constitute originality creativity or acceptable ideas To speak concisely and deliberately with interest and original thoughts to be *followed through* later is a quality rarely manifested at meetings and by committees

A decision of a committee is a decision without individual responsibility Who knows who is to be held responsible for failures and errors of committee decisions? No one on the committee can be challenged or held accountable In such instances of questionable decisions the chairman merely states that the decision was that of the committee and that he is not responsible Such is the reply of each member and of whoever appointed the committee The committee is without reproach, responsibility or contestability But the decision remains and must prevail regardless. After all, it *represents* the "democratic" process Nevertheless committees *are to a* nation what an absence of free enterprise is to a nation — "no incentive Eliminate free enterprise and *incentive is* lost employ committeeism and incentive is lost

Such characteristics can never be found simultaneously in one man. An individual is at least accountable and can be approached for recourse and *is one in whom* direct evidence of responsibility resides Select an able man give him authority and responsibility *and the results* will be good To know the qualities of an able man reflects genius and to recognize an able man *is* the *privilege* and ability of only a few But to benefit from his efforts is the good fortune of many

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The calculation of the mean pressure gradient in aortic valvular stenosis A simplified approach

Recently it has been reported that mean ejection pressure (MEP) could be reliably calculated using either of two simple formulas [1] The first method consists of calculating MEP from peak systolic and aortic valve closure pressures (a and b in Fig 1 A respectively) as expressed in Equation 1 below

$$\text{MEP} = a - (a\ b)/3 \qquad (1)$$

The second approach uses aortic end diastolic pressure (c in Fig 1 A) and a as given in Equation 2 below

$$\text{MEP} = c + 0\ 8(a\ c) \qquad (2)$$

These formulas were derived and tested for over 350 observations in man dogs and calves over a wide range of mean arterial and pulse pressures and heart rates and were found to be quite accurate when compared to MEP computed by integration ($r > 0\ 98$)

The question has arisen whether this method would also prove valid for calculating the mean pressure gradient (mean Δ P) across the aortic valve in the presence of aortic valvular stenosis In aortic stenosis mean Δ P *is derived by the* subtraction of left ventricular and aortic mean ejection pressures (i e MEP minus MEP as shown in Fig 1 B) If we calculated MEP and MEP separately as in Equation 2 using a or peak systolic ventricular *pressure* a, *or* aortic peak systolic pressure respectively with c (see Fig 1 B) by

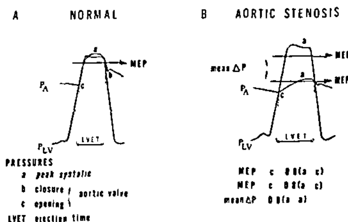


Fig 1 **A** and **B** *A Mean ejection pressure (MEP) in normal* subjects *B* The calculation of mean ejection pressure (mean ΔP) in aortic stenosis See text

subtracting *these expressions the resulting equation would* be found

$$\text{mean } \Delta P = \text{MEP}' - \text{MEP} = 0\ 8\ (a\ a) \qquad (3)$$

From this expression the mean Δ P may be calculated simply by taking eight tenths the difference of ventricular

Ebstein s anomaly

To the Editor

Sekelj and Benfey report (Historical landmarks Ebstein s anomaly of the tricuspid valve AM HEART J 88 108 1974) that the first case diagnosed during life was reported by Van Lingen and her colleagues in 1952 This is incorrect Zatuchni Stauffer and I reported a woman with this anomaly in 1951 (*Am. J Med. Sci.* 222 554 1951) This report was originally sent to *Circulation* almost immediately after Engle and her colleagues reported three cases found at au topsy The reviewers rejected our report because there was no proof of the diagnosis. Our report fulfilled all of Engle s criteria and, in addition, described a hitherto and otherwise unexplainable pathognomonic sign of Ebstein s anomaly

It is regrettable that the patient died several years later after an unsuccessful operation to correct a lesion that was not present. Dr Charles C Wolferth called me to congratu late our group on the diagnosis that had been made years previously and he was also kind enough to send us the heart. A picture and description of the heart is reported in the *American Journal of Medical Sciences* 233 23 1957

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Reply

To the Editor

It is good that Dr Soloff and colleagues should establish their right to the first description of Ebstein s anomaly to be made during life They win by a short head since their paper was published in November 1951 two months before the paper of Van Lingen and colleagues appeared in the AMERI CAN HEART JOURNAL. Both groups deserve our congratula tions

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Letters to the Editor

Opening snap in mitral stenosis

To the Editor

Thank you for providing us an opportunity to reply to the letter of Dr Rodbard (Am Heart J 88 677 1974) regarding the opening snap in mitral stenosis We believe that this sound is indeed an opening snap and that it occurs at the moment that the valve achieves its fully open position and comes to a sudden halt This traditional view of its genesis is supported by combinations of echo and phonocardiographic tracings

In our earlier studies of echo sound phenomena we used an analog gating device which permitted the demonstration of the movements of the anterior leaflet of the mitral valve as a single line The method was useful but technically difficult. It inevitably produced artifacts with sudden notches and unexplained flat portions of the curve For these reasons we have for some time discontinued the analog gating technique and use exclusively the strip chart recording method shown in the accompanying illustration (Fig 1) The sudden closing movements mentioned by Dr Rodbard are we feel sure artifacts of the analog gate method and should be disregarded

In the more modern strip chart echocardiograms[1] the clear and reproducible relationship between the opening snap and the achievement of a fully open position of the valve is illustrated This relationship has been unvarying in our experience and supports the classical explanation for the genesis of the opening snap

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REFERENCE

1 Craige E. and Fortuin, N J Genesis of heart sounds and murmurs as demonstrated by echocardiography *in* Joyner C ed Ultrasound in the diagnosis of cardiovascular pulmonary disease Chicago 1974 Year Book Medical Publishers p 122 Fig 7 2

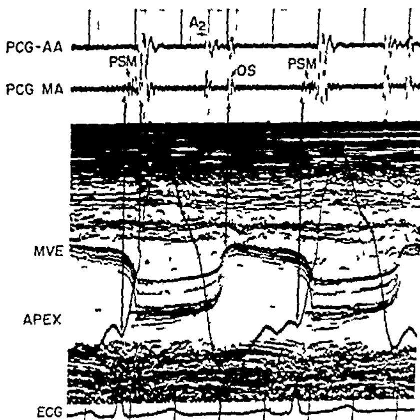


Fig 1 Mitral stenosis A combined phono echocardiogram demonstrating the relationship between the apexcardiogram valve movements and auscultatory phenomena In early diastole the mitral valve opens and the opening snap is seen to occur at the culmination of the anterior movement of the valve Timeslines = 0 04 sec (From Craige E and Fortuin N J Genesis of heart sounds and murmurs as demonstrated by echocardiography *in* Joyner C R ed Ultrasound in the diagnosis of cardiovascular pulmonary disease Chicago 1974 Year Book Medical Publishers p 122 Used by permission)

calculating data measuring cardiac output and shunts types of catheters complications assessment of results and clinical applications are among the many important aspects of the subject discussed. The many actual photographs of roentgenographic films obtained for common cardiac disease states and included in the atlas are excellent and the accompanying legends good and represent a valuable feature of the book. All cardiologists as well as trainees will find this highly recommended publication worth owning

Books received

Physiology and Biophysics vol II Circulation Respiration and Fluid Balance 20th ed Edited by Theodore C Ruch Ph D and Harry D Patton Ph D M D Philadelphia 1974 W B Saunders Company 558 pp $17 50

Hypertension vol XXII Papt des Lipids Electrolytes and Hypertension Proceedings of the Council for High Blood Pressure Research American Heart Association Cleveland Ohio October 19 and 20 1973 New York, 1974 American Heart Association Inc 224 pp $5 00

Health Hazards of a Western Diet By George A. Stanton B A M B Ch.B Cambridge England, 1974 F & P Piggott, Ltd 115 pp

Platelets and Thrombosis Edited by Sol Sherry M D and Alexander Scriabine M D Baltimore Md. 1974 University Park Press 307 pp $14 50

Planning for Cardiac Care A Guide to the Planning and Design of Cardiac Care Facilities By Colin W Clipson and Joseph J Wehrer Ann Arbor Mich 1974 The Health Administration Press The University of Michigan 381 pp

Care of the Critically Ill 2nd ed By Stephen M Ayres M D Stanley Giannelli Jr M D and Hiltrud S *Mueller M D* Englewood Cliffs N J 1974 Appleton Century Crofts, Prentice Hall Inc 345 pp Price $12 50

Lupus Erythematosus Edited by Edmund L Dubois M D Los Angeles 1974 University of Southern California Press, 646 pp Price $36 00

Evaluation of Drug Interaction 1st ed and 1974 supplement Washington, D C 1974 American Pharmaceutical Association.

Role of catecholamines in cardiovascular diseases I Hypertension By Budh Dev Bhagat Springfield Ill 1974 Charles C Thomas Publisher 200 pp

This book summarizes very well the physiology and pharmacology of the role of the catecholamines in arterial hypertension The antihypertensive agents currently used in therapy are so closely related to the subject of this publication that physicians will find the book helpful The author has simplified the concepts for the busy student and physician Hypertension is still one of the most important diseases of man It is readily controlled provided the physiology is clearly understood. There are simple illustrations which review the mechanisms considered responsible for the hypertension and its many associated manifestations These all relate to treatment Diagnosis and treatment are considered. This is a good book for teaching It should interest not only physicians but undergraduate medical students as well

Electrocardiography and related coronary care A complete manual for the nurse By Victor E Schulze Jr M D Garden Grove Calif 1974 Trainex Press Trainex Corp 248 pp

This manual is intended for nurses who work closely with cardiac patients The discussions and illustrations are made simple for beginners but as shown in Figure 2 5 they can be too simple In this illustration for example the author fails to label the tracings due to anterior and posterior infarction Nevertheless with the assistance of cardiologists the nurse can find the book useful The need for supplemental assistance from physicians is again illustrated on page 29 where the vectorcardiogram is described Regardless nurses will find many interesting and valuable bits of useful information in this manual To appreciate fully the importance of the information the nurse must think and study other publications as well This is a good and useful manual

Lecture notes on cardiology By J S Fleming M D M R C P and M V Braimbridge M A M B Oxford London Edinburgh Melbourne 1974 Blackwell Scientific Publications 326 pp

This second edition of this book on clinical cardiology should interest all general practitioners internists and clinical cardiologists The authors a cardiologist and cardiothoracic surgeon summarize clinical cardiology and cardiac surgery from the practicing physician s point of view The illustrations are simple and clear In fact some of the illustrations may be even too simple such as Figure 2 2 on page 90 of atrial flutter Nevertheless the illustrations do present the concept effectively for the beginner or less experienced cardiologist The subjects discussed are remarkably extensive for a book of about 300 pages This is a good book which is highly recommended to busy general practitioners and internists It is designed to promote better bedside cardiology

Systemic arterial hypertension By Milton Mendlowitz M D F A C P F A C C P Springfield Ill 1974 Charles C Thomas Publisher 189 pp

Mendlowitz has been interested in systemic arterial hypertension for many years He has personally contributed to the field particularly the relationship of the behavior of the peripheral circulation to hypertension This book condenses his many ideas and contributions very effectively His preface listing contributors to the field, is an interesting part of the book The material considered is both physiologic and clinical There is greater emphasis on the clinical syndrome and pharmacology than on the mechanism responsible for hypertension This small book of about 100 pages should interest all physicians concerned with the treatment of hypertension An extensive bibliography is appended to the book

Recent advances in studies on cardiac structure and metabolism Vol 4 Myocardial biology Edited by N S Dhalla. Baltimore 1974 University Park Press 614 pp

Volume 4 continues the excellent series of publications on cardiac structure and metabolism The book contains a series of papers on the electrical and mechanical properties of heart membrane transport, and calcium metabolism and heart function The latter is discussed extensively This book should interest biochemists, biophysicians physiologists and pharmacologists Clinicians will find the discussions extremely valuable but complex for those who have failed to follow the biochemical and physiologic literature The importance of this book cannot be overemphasized Dhalla and Rona have accumulated an interesting series of presentations for those interested in the myocardium The myocardium certainly needs extensive considerations and support in research and teaching This book contains some of the interesting investigations in progress

Symposium on digitalis Edited by Ole Storstein in collaboration with Sigurd Nitter Hauge and Liv Storstein Oslo 1973 Gyldendal Norsk Forlag 428 pp Price $25 00

This book includes the presentations on digitalis from a conference held in Oslo during February 1973 The conference was mainly concerned with metabolism and kinetics of digitalis distribution throughout the body Digoxin was the preparation considered most The action of digitalis was thoroughly discussed but just how to use digitalis in clinical practice received very little consideration Although there was a great deal of attention to digitalis intoxication the clinician who reads this book will find little advice as to how to use the drug and achieve full digitalization without intoxicating the patient Satisfactory digitalization is done routinely by any master internist or master cardiologist Pharmacologists will find this to be a useful book whereas the practicing clinician will find little of practical use to him except those aspects related to digitalis intoxication and the difficult problems related to the use of digoxin

Cardiac catheterization and angiocardiography An introductory manual ed 2 By David Verdel and Ronald G Grainger Foreword by Sir John McMichael Edinburgh and London 1973 Churchill Livingstone 228 pp

This book describes the techniques of cardiac catheterization and angiography for beginners The authors rightly emphasize the importance of adequate and acceptable standards of recording In many laboratories the emphasis on accuracy is too often neglected The principles concerned with

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Editorial

The epidemiological emergence of ischemic arterial diseases

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A recent study from Uganda indicated that in an African population pursuing a primitive existence—consuming a frugal nonrich diet and leading a physically active manner of life—the elderly die not from degenerative diseases but from mainly preventible causes i e from diseases of childhood, such as infections acute tuberculosis neglect and malnutrition [1] A leading article on The aged ailing African taking into account the foregoing and other evidence concluded that even in the aged African degenerative cardiovascular disease is of little importance thus ischemic heart disease arteriosclerosis and other cardiovascular conditions so common in elderly Whites remain uncommon in the elderly Ugandan as elsewhere in Africa [2] This situation strongly contrasts with that in western populations For example in Australia in 1970 among persons under 65 years of age coronary heart disease (CHD) plus cerebral vascular disease (CVD) accounted for almost half (44 per cent) of all deaths [3]

What are the *minimum* sequelae of aging in respect to atherosclerotic lesions of the vascular system and the associated diseases CHD CVD and peripheral vascular disease (PVD) ? Further more in developing populations *in what order* and to what extent epidemiologically do these diseases emerge with rise in socioeconomic circumstances?

The first question although in respect of cancer was raised by Higginson [4] For each site, he obtained data on the minimum frequency (age specific) Thus he selected the United States for cancer of the liver an African population for cancer of the lung and so forth Higginson concluded that in a hypothetical population with the lowest possible incidence cancer incidence would be approximately one third of that observed in the United States In approaching atherosclerosis and its lethal sequelae in this manner the first that must be recognized is that in parts of rural Africa atherosclerosis and other factors promotive of arterial diseases (principally hypertension) are sufficiently minimal and that CHD CVD and PVD scarcely occur at all [1,5]

Extensive necropsy studies on populations at various stages of sophistication have revealed that with rise in prosperity different parts of the vascular bed age or develop lesions at different rates [6,8]

The first arterial disease of clinical significance to emerge is cerebral vascular disease In Uganda death from this cause remains rare especially in rural areas [1] Even in Khartoum a city in the Sudan it was found that at the teaching hospital of 581 necropsies undertaken on adults

From the Medical Research Council Human Biochemistry Research Unit, South African Institute for Medical Research Johannesburg South Africa

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Reprint requests to Dr Alexander R P Walker Medical Research Council, Human Biochemistry Research Unit, South African Institute for Medical Research, Johannesburg South Africa

Infectious diseases 1975 Treatment and prevention

The Mount Sinai Medical Center Cedars of Lebanon Health Care Center and the University of Miami School of Medicine are sponsoring the fifth annual seminar on the treatment and prevention of infectious diseases The seminar will be held at the Hyatt House Hotel Ocean front at 54th St. Miami Beach Fla from January 9 through January 11 1975 The fee for physicians and hospital administrators is $100 the fee for nurses and paramedical personnel is $50

For further information regarding this seminar please contact Minver S Reed Coordinator Continuing Medical Education Mount Sinai Medical Center 4300 Alton Rd. Miami Beach Fla 33140

Thromboembolism Diagnosis and treatment

The American Heart Association Council on Thrombosis the Florida Heart Association and the Heart Association of Greater Miami are sponsoring a seminar on the diagnosis and treatment of thromboembolism to be held at the Doral Beach Hotel Ocean front at 48th St. Miami Beach Fla from February 27 through March 1 1975 The fee for members of the Council of the American Heart Association is $100 the fee for non members is $150 For further information please contact George E. Stewart Jr American Heart Association 44 E 23rd St New York N Y 10010

Training Program in Pediatric Cardiology

The Helen B Taussig Children s Cardiac Center of The Johns Hopkins Hospital is offering a new three year training program in pediatric cardiology to train skilled clinicians and teachers and to make original research contributions in the field of cardiovascular disease

The first year is designed to develop competence in diagnosis and management In the second and third years the following research interests may be pursued during three separate periods of study either within the division of pediatric cardiology or in other areas of The Johns Hopkins University atherosclerosis lipid metabolism hypertension electrophysiology embryology and pathology epidemiology genetics hemodynamics myocardial metabolism neonatology and intensive care unit, pharmacology pulmonary disease ultrasonics and rheumatic heart disease Trainees will work in the laboratories of the directors of the various research disciplines and will take selected courses offered by The Johns Hopkins University

Candidates will be medical graduates with a minimum of two years experience in general pediatrics They should be American citizens or have an immigrant visa and have passed the ECFMG Interested parties should contact Glenn C Rosenquist M D Acting Director Helen B Taussig Children s Cardiac Center CMSC 239 The Johns Hopkins Hospital Baltimore Md 21205

Fourth World Congress on Ballistocardiography

The fourth World Congress on Ballistocardiography and Other Non invasive Methods in Cardiovascular Dynamics will be held in Amsterdam The Netherlands on April 14 through 16 1975 The congress organized by the Physiological Laboratory Free University van der Boechorststraat 7 Amsterdam is open to members of the European and American Societies for Ballistocardiography and Cardiovascular Dynamics as well as to all clinicians physiologists and physicists working on or interested in cardiovascular dynamics

Each session will open with an invited lecture to be followed by free communications Subjects discussed will be the relation of invasive and non invasive mechanical methods evaluation of non invasive methods and their possible use for the early detection of ischemic heart disease influence of therapeutic measures on ischemic heart disease evaluated with non invasive methods data analysis of ballistocardiographic recordings improvement of non invasive techniques such as three plane ballistocardiography carotid pulse etc use of non invasive methods in studying cardiovascular aging processes Delegates wishing to contribute a paper should send their abstracts to the scientific committee before January 1 1975 For further information regarding the congress please contact Dr W J A Goedhard, Secretary Physiological Laboratory Free University P O Box 7161 van der Boechorststraat 7 Amsterdam The Netherlands

World Congress on Electrocardiology

The World Congress on Electrocardiology will be held on February 28 through March 2 1975 at the Oberoi Sheraton Hotel Bombay India For further information please contact Dr A B Mehta World Congress on Electrocardiology" Department of Electrocardiology L. T M Medical College Sion Bombay 400022 India

International symposium on intensive therapy

An international symposium on intensive therapy stressing total parenteral alimentation co sponsored by the Italian Society of Anesthesiology and Recuperative Care and by the Society for Critical Care Medicine will be held in Rome Italy from May 30 1975 through June 2 1975 President of the symposium is Dr Corrado Manni round table moderators will be Drs. Raffaello Breda Stanley J Dudrick, Robert M Filler Alessandro Gasparetto Alan Gilston Giuseppe Giunchi Peter Safar Giuseppe Segni William C Shoemaker and Sergio Stipa Topics for round table discussions will be Experimental and metabolic aspects of total parenteral alimentation Clinical evaluation of total parenteral alimentation in the medical patient Clinical evaluation of total parenteral alimentation in the surgical patient Clinical evaluation of total parenteral alimentation in pediatrics and Indications techniques and complications Guided sightseeing of Baroque Rome and an excursion to the Villa Adriana and the Villa D Este are an added part of the program

Symposium participants who wish to present communications films or exhibits of scientific material related to the topics covered are requested to file abstracts (300 words or less) and other data with the Organizing Secretariat New Media Via G B Martini n 6 00198 Rome Italy by January 31 1975 Presentations are limited to 8 minutes Registration fees for the symposium will be 50 000 Italian lire before Jan 31 1975 and 75 000 Italian lire after Jan 31 1975 Hotel reservations must be made before Jan 31 1975 and will require a deposit of 20 000 Italian lire

For forms and all information regarding the symposium please write International Symposium on Intensive Therapy New Media Via Giovanni Battista Martini 6 00198 Rome Italy

South African Negroes of 60 or more years prevalences of impalpable pulses of the posterior tibial and dorsalis pedis arteries were found to be 3 and 5 per cent respectively [27] In England, in a hospital population of the same age in patients not admitted for vascular diseases the corresponding prevalences were reported to be 16 and 17 per cent respectively [28] Results of studies on pulses in random series of elderly populations differing in race and level of privilege but using the more accurate ultrasonic method,[29] would be illuminating Among South African Negroes in Johannesburg in hospital practice PVD is very uncommon in males and rare in females when present the disease occurs chiefly in males with diabetes and in those who are heavy smokers [30] In the United States no investigations appear to have been carried out to determine comparative PVD rates in representative series of Negroes and Whites In a study of intermittent claudication at Framingham it was maintained that The natural history of peripheral occlusive arterial disease needs to be better defined Incidence data on occlusive peripheral arterial disease in general population samples are simply not available [31] In the Framingham investigation average annual incidence rates for White men and women aged 55 to 64 years were 53 and 18 per ten thousand respectively In England it has been claimed that chronic ischemia due to PVD is one of the most common conditions seen in clinical practice [32] Currently in westernized populations it is not known whether prevalence or incidence of PVD is increasing steady or decreasing There are some items of comparative information on White populations available from other parts A study undertaken in Israel showed that the rate for PVD among immigrant Jews from North Africa was about a fifth of that of Jewish immigrants from Eastern Europe [33] In Greece in an enquiry into PVD among rural populations the occurrence of the disease was stated to be extremely low CHD was also uncommon [34] As a cause of mortality the health hazard from PVD lies principally in its association with an increased mortality from CVD and CHD [32]

Briefly in an African developing population of diseases consequent on an increasing severity of atherosclerosis and other promotive factors the first to emerge is CVD Among Negroes in Africa in some large urban centers, mortality rate from CVD principally from cerebral hemorrhage reaches and then exceeds that of White populations Among Negroes in the United States the proportion of total deaths due to CVD has risen to about 13 per cent CHD with rise in prosperity emerges much later than CVD in sophisticated African Negro populations CHD still remains a negligible cause of death Among Negroes in the United States in some segments CHD mortality approaches that of Whites among whom it causes about 30 per cent of all deaths PVD virtually absent in populations living primitively increases in prevalence with rise in privilege As a clinical problem it emerges somewhat before CHD

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over the period 1957 1969, CVD was the cause of death in only four patients[9] This situation contrasts with that in the township of Soweto, Johannesburg, South Africa, where the most highly urbanized of African Negro populations, about three quarters of a million, reside In a necropsy study on corresponding series of Negroes and Whites it was found that in gradings made of cerebral arteries scores were much lower for Negroes than for Whites[7,8] Yet, in Johannesburg in 1960, of total deaths the age specific percentage from CVD was slightly higher for Negroes than for Whites[10] However, the deaths among Negroes from CVD were seldom due to infarction or thrombosis but mainly due to cerebral hemorrhage associated with high blood pressure which inexplicably is very common among Negroes in large centers of population[11] In the United States one necropsy study revealed that Negroes had more atherosclerosis in the intracranial arteries and as much or more in the cervical arteries while Whites had more atherosclerosis in the aorta and coronary arteries It was maintained that these findings paralleled mortality rates from CVD and CHD[12] In an investigation on CVD made in Evans County, Ga it was found that the age specific prevalence rate of stroke' was higher in Negroes than in Whites, the rate being almost three times greater in Negro than in White women[13] In 1960 1961 in the United States CVD accounted for about 11 and 13 per cent of total deaths of Whites and Negroes respectively[14] As to trends in mortality rate, in many White populations there have been reductions mainly from anti hypertensive treatment, during the period of the last generation[15,16]

In the coronary vessels, with rise in sophistication, lesions of clinical significance are slower in becoming manifest In many parts of Africa, CHD in Negroes does not occur It has been stated that ' Nigerians arteries are smooth as velvet, and that 'coronary heart disease is virtually nonexistent even in the bustling capital of Lagos[17] In Accra (population about 350,000), 10 patients with CHD were seen at the teaching hospital between 1968 and 1970[18] In Johannesburg in a study reported in 1954 it was shown that Negroes had less aortic and coronary atherosclerosis than Whites[19] This finding was confirmed in a later necropsy series in which it was stated that 66 per cent of coronary arteries in Negroes showed no lesions[7] In the remainder lesions were composed almost exclusively of lipid streaks and fibrous plaques, neither ulceration nor hemorrhagic lesions were seen In a similar investigation, pursued at Pretoria it was noted that even before the second decade, aortas and coronary arteries of White subjects were more affected than the same vessels in the Negroes[8] As to deaths of Negroes from CHD it is considered that, in Johannesburg there are less than twenty *per annum*, yet in a local White population of the same age and sex structure about 1 200 sudden deaths or episodes would be expected.[20] In Evans County, in studies made on cardiovascular disease, it was reported that White males had an age adjusted prevalence rate almost three times higher than for Negro males, although no differences were found by ethnic group for females[21] However, the United States National Survey indicated a much smaller disparity of CHD in males[22] Among Whites in the United States the disease now accounts for about 30 per cent of all deaths[23] South African Negroes in time will undoubtedly experience increases in the occurrence of CHD Nevertheless it is unwarranted to assume that as increase in prosperity and rise in privilege occur, CHD mortality rate in these people will inevitably reach that of United States Negroes Not only do Southern African Negroes and American Negroes differ ethnically and genetically, but even among White populations exposed to outwardly equally high socioeconomic circumstances there are widely different mortality rates from CHD, e g that in Scotland is about four times higher than the corresponding figure for France[23] While the mortality rate from CHD appears to have reached a plateau in the United States and some European countries it is still rising in others[23,24]

Epidemiologic information on the natural history and emergence of peripheral vascular disease is meager, in comparison with that available on CVD and CHD As with these diseases PVD is extremely uncommon in rural African populations[5] Among Negroes in Rhodesia it has been stated that PVD is rarely seen[25] This is also the case among South African Negroes in country areas[26] In Johannesburg in a necropsy study on Negroes, it was reported that 'Atheroma of the peripheral vessels is rarely seen even in the presence of significant aortic and iliac atheroma '[7] In a pilot study on rural

Clinical communications

Serial hemodynamic observations in congenital valvular and subvalvular aortic stenosis*

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Gita T Mody MD
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Relatively little is known about the natural history of valvular and subvalvular aortic stenosis There is always a question of whether a case of mild aortic stenosis will become more significant as age advances and what the outcome of a moderate or severe lesion will be It is also of interest to determine whether the behavior of subvalvular aortic stenosis at follow up is any different from that of valvular aortic stenosis The purpose of this study is an attempt to advance some ideas about the evolution of hemodynamic changes in valvular and subvalvular aortic stenosis which might help us to outline the prognosis in a given case with varying severity

Material and methods

The material consists of 28 patients with aortic stenosis seen at Henry Ford Hospital (Tables I and II) Twenty two of these were isolated valvular stenosis cases and six were subvalvular membrane stenosis cases All of them had clinical signs of left ventricular obstruction and a minimum peak systolic pressure gradient of 15 mm Hg across the aortic valve or the subvalvular area Patients with associated lesions were not accepted. Each of these 28 patients had an initial and a repeat cardiac catheterization without intervening surgery Thus 56 cardiac catheterizations were performed on 28 patients The left ventricle was entered in all cases by the retrograde arterial route Right heart catheterization was done in 44 of the 56 studies

Age The age distribution at initial and repeat cardiac catheterizations is also shown in Tables I and II In patients with valvular stenosis the minimum age at the initial study was four months maximum 13 years and mean 4 7 years At the repeat study the minimum age was 4 5 years maximum 19 5 years and mean 11 6 years. The group with subvalvular aortic stenosis had a minimum age at the first study of seven weeks maximum age of 10 years and an average age of 3 8 years At the repeat study the minimum age was one year maximum 15 years and mean 8 1 years An average interval between studies in valvular aortic stenosis was about 6 7 years and in subvalvular aortic stenosis about 4 2 years.

Sex Of the 22 patients with valvular stenosis five were females and the remaining 17 were males The relatively high incidence of aortic stenosis in males has also been documented by Friedman and Braunwald[1] and Nadas and Fyler [2] Of the six patients with subvalvular aortic stenosis there were three males and three females

Symptoms None of the 22 patients with valvular aortic stenosis were symptomatic at the initial study At the repeat cardiac catheterization six of the 22 patients had mild symptoms of easy fatigue and dyspnea on exertion None of the patients had fainting episodes chest pain or congestive heart failure Out of the six patients with subvalvular aortic stenosis three patients were symptomatic at the initial study and also at the repeat study Two of these patients had easy fatigability dizziness and chest pain as well as dyspnea on exertion In one patient congestive heart failure was noted at the time of the first study but this had improved by the time the second study was performed.

X ray examination The x rays in valvular aor

From th Henry F rd Hosp tal, Detroit.
Rec ed for publication March 21 1974
Reprint requests D Madhu R. Mody Ped: tric Ca diology H nry Ford Hosp tal, 2799 W Grand Bl d D tro t, M ch 48202
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Table II Observations in subaortic stenosis

Case No	*Age (yr)*	*LV pressure (mm. Hg)*	*Subvalvular pressure (mm. Hg)*	*Peak Systolic gradient (mm. Hg)*	*Cardiac index (L./min./M²)*	*Aortic angiogram*	*ECG*	*Surgery*
1	7	190/10	118/5	72	3 4	N	N	
	9	210/20	130/20	80	4 2	–	LVH & ST T	Yes
2	1	120/16	90/12	30	3 7	–	N	
	4½	165/15	115/12	50	–	–	LVH & ST T	Yes
3	10	150/10	110/10	40	4 6	–	N	
	15	165/6	120/4	45	3 0	Mild AR	LVH & ST T	Yes
4	4	200/10	110/10	40	4 0	–	LVH	
	10	212/11	112/0	100	3 5	–	LVH & ST T	Yes
5	1	130/19	98/19	32	4 4	–	LVH	
	9	244/27	154/27	90	3 7	–	LVH & ST T	Yes
6	7 wks	220/10	92/10	128	5 0	–	N	
	1	250/34	75/32	175	3 8	–	LVH & ST T	Yes

AR = aort c regurg tati n
LV – left e tricl
LVH = left entr ular hypertrophy
N = n mal
ST T = ST d pre ion and T wave n rs n.
wks = weeks
yr – years
– – not pe form d.
Observat ons n subaort sten is

group was six years old. In the group with sub valvular stenosis five had normal x rays while one had radiologic findings of congestive heart failure at the first study which cleared up with treatment and heart size was normal when the second study was performed No poststenotic dilation was seen in this group

Electrocardiogram All the patients had a twelve lead scalar electrocardiogram recording at the time of initial and repeat cardiac catheterization (Tables I and II) The values for normal and for left ventricular hypertrophy by voltage as described by Nadas and Fyler[2] were used At the first study the electrocardiogram was within normal limits in 21 of the 22 patients with valvular aortic stenosis There was only one patient with left ventricular hypertrophy as seen by an increase in voltage At repeat cardiac catheterization only 15 patients had normal electrocardiograms and in 5 of these 15 cases although the left ventricular voltage had increased, it was still within the normal range Two cases had left ventricular hypertrophy by voltage and five in addition to increase in voltage had ST and T wave changes These findings indicate that there were six patients who had significant changes on the electrocardiogram between the first and the second studies In the six patients with subvalvular aortic stenosis four patients had a normal electrocardiogram at the first study and two patients had left ventricular hypertrophy by voltage At the repeat study all the patients had significant left ventricular hypertrophy by voltage and had now developed ST and T wave changes Although our series is small we can predict that subvalvular aortic stenosis is a more progressive disease than valvular stenosis of comparable severity

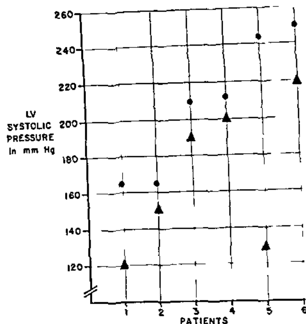
Hemodynamic data Hemodynamic data are again shown in Tables I and II and Figs 1 and 2 Right heart catheterization was performed in a total of 44 studies out of 56 No shunts were demonstrated in any of these studies The right sided pressures were normal in all patients except one with subvalvular aortic stenosis (Case No 6 Table II) This infant was seven weeks old at the time of initial study and had a pulmonary artery pressure of 65/20 mm Hg On repeat study at the age of one year the pulmonary artery pressure was still elevated to 58/25 mm Hg The left ventricular pressure and the peak systolic gradient between the left ventricle and aorta were obtained in each and every study The highest peak systolic left ventricular pressure was 240 mm Hg in the group with valvular aortic stenosis and 250 mm Hg in patients with subvalvular aortic stenosis For the purpose of simplification we have classified these patients into three groups according to their peak systolic left ventricular to aortic pressure gradient (1) those with mild stenosis had a pressure gradient of <50 mm Hg (2) those with moderate stenosis had a pressure

Table I Observations in aortic valvular stenosis

Case no	Age (yr)	LV pressure (mm Hg)	Aortic pressure (mm. Hg)	Peak systolic gradient (mm. Hg)	Cardiac index (L/min/M²)	Aortic angiogram	ECG	Surgery
1	3	126/14	88/58	38	3 9	–	N	
	11½	180/30	120/86	60	4 5	Mild AR	N	Yes
2	13	166/24	104/80	62	5 5	–	N	
	19½	160/16	115/75	45	–	–	N	No
3	4½	130/10	102/78	28	4 4	N	N	
	8	138/10	106/76	32	4 6	Mild AR	N	No
4	4½	140/10	98/60	42	4 0	–	N	
	13½	170/14	100/80	70	4 1	N	LVH & ST T	Yes
5	1½	150/10	94/60	56	4 1	–	N	
	8	200/14	120/90	80	3 6	–	LVH & ST T	Yes
6	8/12	120/16	74/50	46	4 1	–	N	
	13	185/5	80/60	105	4 8	N	LVH & ST T	Yes
7	6/12	162/16	94/56	68	5 1	–	N	
	11	220/5	120/75	100	–	–	LVH & ST T	Yes
8	8½	170/20	80/60	90	4 5	–	N	
	11	195/10	95/65	100	–	–	N	Yes
9	2	98/14	74/44	24	5 2	–	N	
	12½	180/15	120/85	60	–	–	N	No
10	2	154/4	76/50	78	5 1	–	N	
	11	190/16	120/92	70	3 5	Mild AR	N	No
11	12	130/20	100/64	30	5 0	–	N	
	18	140/20	100/74	40	3 9	–	N	–
12	5/12	160/10	90/62	70	–	–	LVH	
	4½	150/20	100/60	50	–	Mild AR	LVH	No
13	1	160/14	110/70	50	–	–	N	
	7	140/10	95/75	45	–	–	N	No
14	4/12	170/24	110/70	60	3 4	–	N	
	7	240/18	114/90	126	3 5	N	LVH & ST T	Yes
15	4	130/10	82/54	48	5 0	–	N	
	7	176/20	88/65	88	5 4	N	N	Yes
16	7	146/12	104/70	42	4 4	–	N	
	11	200/16	104/80	96	4 4	–	N	Yes
17	12	120/18	100/80	20	4 5	Mild AR	N	
	17	180/12	140/100	40	–	–	N	Yes
18	6	136/10	90/68	46	4 25	–	N	
	12	230/12	130/80	110	–	N	LVH	Yes
19	3½	98/10	80/48	18	3 9	–	N	
	13½	158/12	110/80	48	6 1	–	N	No
20	7	160/26	120/90	40	4 4	–	N	
	14	142/16	126/81	16	4 5	Mild AR	N	No
21	4½	140/10	80/56	60	5 7	–	N	
	11	185/20	100/80	85	–	–	N	Yes
22	5½	150/12	106/68	44	3 3	–	N	
	14	148/10	118/74	30	6 1	Mild AR	N	No

Observations in aortic valvular stenosis
AR = aortic regurgitation
LV = left ventricle
LVH = left ventricular hypertrophy
N = normal
ST T = ST depression and T wave inversion
yr = years
— = not performed.

tic stenosis revealed that there was no cardiomegaly in any of the patients either at the initial or the repeat cardiac catheterization An interesting finding was that poststenotic dilation of the ascending aorta was present in only five patients at the first study but was present in 15 patients at the repeat study These findings suggested that poststenotic dilation was an acquired manifestation which occurred with time The youngest child with poststenotic dilation in this



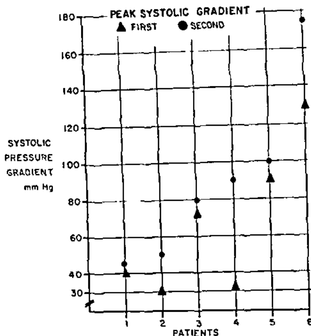
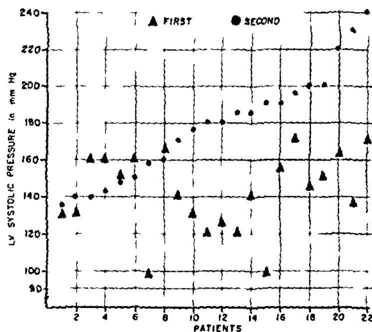


Fig 2 left and right Graphic representation of the serial hemodynamic data of the six patients with subvalvular aortic stenosis LV = left ventricle ▲ First ● second.

with serial hemodynamic studies one to two years after the first study and it was mentioned that there was an increase of between 20 and 40 mm. Hg gradient in three of these four cases Bandy and Vogel[5] recorded one case who at the age of five years had a pressure gradient of about 21 mm Hg across the aortic valve and this had increased to a gradient of 103 mm Hg at the age of 12 years Cohen Friedman and Braunwald[6] reported serial hemodynamic observations in 15 patients with aortic stenosis nine of whom became more severe at follow up study and six of these were of sufficient severity to warrant operation El Said and co workers[7] reported serial hemodynamic observations in 18 patients with valvular aortic stenosis and in six patients with discrete subvalvular aortic stenosis In their experience the majority of patients with valvular and subvalvular stenosis increased in severity The change was more severe with subvalvular than with valvular stenosis In only one of their six patients with subvalvular aortic stenosis did the severity fail to change significantly and this patient had a pressure gradient greater than 50 mm. Hg at the first study Only 18 months separated the two studies Cohen and co workers[8] reported 18 patients with valvular aortic stenosis and found increasing severity in one third of these at a follow up study five to seven years later Hurwitz[9] reported 19 patients with valvular aortic stenosis with serial hemodynamic observations Of these 19 patients 12 were mild cases 5 were moderate cases and 2 were severe cases at the initial study At follow up 11 cases remained mild, 4 cases had moderate stenosis and the remaining 4 cases had severe stenosis In his opinion mild stenosis seldom progresses enough during childhood to necessitate surgery Of the 29 patients reported by Vijayan and co workers[10] nine had a significant increase in gradient four to eight years later while 20 increased by less than 10 mm Hg Our findings are in agreement with most of the authors mentioned earlier In our series of 22 patients with valvular stenosis 13 had an increase in gradient of more than 20 mm Hg at the repeat catheterization three to twelve years later 11 of these being severe enough to require surgery Of the 13 patients who had started with mild aortic stenosis seven progressed to obstruction of surgical significance which is contrary to the experience of Hurwitz.[9]

Aortic regurgitation is a known complication of aortic stenosis and was seen in 53 per cent of our patients who had aortic root angiograms Hohn and co workers[4] reported clinical evidence of aortic regurgitation in 31 per cent of their pa



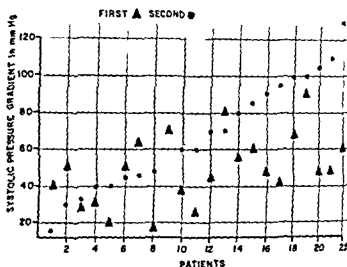


Fig 1 left and right Graphic representation of the serial hemodynamic data of the 22 patients with valvular aortic stenosis LV = left ventricle

gradient between 50 and 100 mm Hg, and (3) those with severe stenosis had a pressure gradient of more than 100 mm Hg It is of interest to note that at the first study there were 13 patients with mild aortic stenosis nine patients with moderate stenosis and none with severe stenosis At the repeat study however, there were only eight patients who had remained mild nine patients were moderate, and five patients had severe stenosis The number of patients with moderate stenosis remained the same because a few of the cases with mild stenosis had now become moderate while some of the cases with moderate stenosis had developed severe stenosis There were no patients in the severe group at the initial study but there were five patients in the severe group at the repeat study which showed progression of the lesion Thus we had 14 patients at repeat study who had moderate to severe stenosis, and 12 of these patients have had successful aortic valvotomies since the second procedure The left ventricular to subvalvular aortic peak systolic pressure gradient in patients with subvalvular aortic stenosis is shown in Fig 2 Of the six patients in this group with subvalvular stenosis there were three mild cases two moderate cases and one severe case at the initial study At the repeat study, there was only one mild case four moderate cases and one severe case Though a significant increase in peak systolic gradient was noted in only two of the six patients, all showed marked left ventricular hypertrophy and strain on the electrocardiogram at the time of the repeat study Surgical resection of the subvalvular membrane was performed in all of the six patients, and two of these patients died in the immediate postoperative period.

Cardiac indexes using an assumed oxygen consumption, were within normal limits in all 44 studies where these were determined. Aortic root angiograms were performed in 15 of the 28 patients, 12 of these were valvular and three were subvalvular Trivial aortic regurgitation was noted in seven of the 12 patients with valvular stenosis and in one of the three patients with subvalvular stenosis No aortic root injections were made in the remaining 13 patients

Discussion

Hemodynamic changes The natural history of congenital valvular and subvalvular aortic stenosis is not well documented Friedman, Modlinger, and Morgan[3] in their recent report mentioned that seven of their nine patients with valvular aortic stenosis increased in severity between two hemodynamic evaluations In their patients the gradient ranged between 15 and 40 mm Hg at the first study and between 20 and 100 mm Hg at the second study Of these nine patients two remained unchanged two developed moderate stenosis, and five became severe Hohn and co workers[4] reported four patients

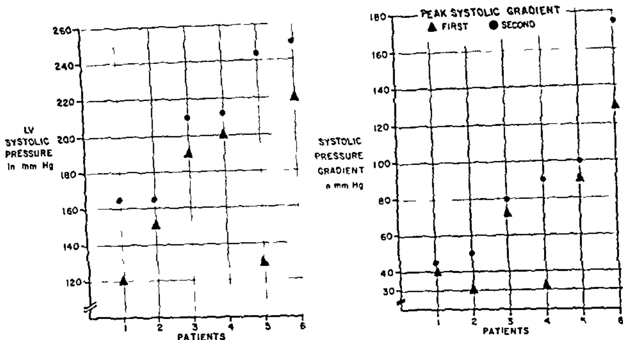


Fig 2 left and right Graphic representation of the serial hemodynamic data of the six patients with subvalvular aortic stenosis LV = left ventricle ▲ First ● second.

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Aortic regurgitation is a known complication of aortic stenosis and was seen in 53 per cent of our patients who had aortic root angiograms Hohn and co workers[4] reported clinical evidence of aortic regurgitation in 31 per cent of their pa

tients with congenital aortic stenosis and found no relation to the anatomic site of the lesion He modynamic study by Hurwitz[9] revealed 10 of the 19 patients had mild to moderate regurgitation at the initial study with significant increase in three patients at a subsequent study four to seven years later On the other hand, Friedman, Modlinger, and Morgan[3] found angiographic evi dence of aortic incompetence in only two of their nine patients and Cohen, Friedman and Braun wald[6] reported it in two out of 15 patients Our experience, like most of the others indicates that in the absence of bacterial endocarditis, the aor tic insufficiency is usually insignificant hemody namically

Electrocardiogram Of the 15 patients reported by Cohen Friedman, and Braunwald[6] eight had normal electrocardiograms at the initial study, six patients had left ventricular hypertrophy by voltage and one patient had left ventricular hy pertrophy by voltage and ST T wave changes At the follow up study there was no significant change in the electrocardiographic findings in these patients Friedman[3] concluded that there was poor correlation between the results of the electrocardiogram and the transvalvular pres sure gradient in any individual patient Cohen and co workers[6] in an unselected population of 18 patients with mild or moderate aortic stenosis found no correlation between the changes in degree of obstruction and in the duration or in tensity of murmur electrocardiogram or chest roentgenogram Hurwitz[9] on the other hand concluded that there was only fair correlation be tween gradient and left ventricular hypertrophy He felt that development of left ventricular hy pertrophy may be a function of time Vijayan and co workers[10] in a group of 29 patients, found no correlation between gradient and electrocar diographic evidence of left ventricular hypertro phy by conventional criteria In our series of 22 patients with valvular stenosis only one patient had left ventricular hypertrophy at initial study, the remaining 21 patients were normal At repeat study, however, two patients had left ven tricular hypertrophy by voltage, and five patients had developed left ventricular hypertrophy with strain Four of the latter had gradients of 80 mm Hg or more On the other hand four other pa tients with similar gradients had persistently normal electrocardiograms Three of these pa tients were operated on immediately, and one pa tient who was observed clinically developed progressive electrocardiographic changes neces sitating surgery three years later Thus, we feel that though an electrocardiogram is helpful in assessing the severity of the lesion, it is by no means conclusive

Sudden death is a much dreaded complication of aortic stenosis and it is important to detect pa tients with severe obstruction since they are most liable to such a catastrophe Most stud ies[11-14] show a good correlation between the inci dence of sudden death and electrocardiogram evidence of left ventricular hypertrophy, with or without strain Ongley and co workers[11] reported four patients who had left ventricular hypertro phy, and two of them had additional ST segment and T wave abnormalities Marquis and Logan[12] reported five cases of sudden death and only one of these five patients died without developing T wave changes in left precordial leads All five of them had left ventricular hypertrophy by voltage On the other hand fatal termination in the absence of any electrocardiographic changes has been reported Braverman and Gibson[15] described a case of aortic stenosis with a normal electrocardiogram who died suddenly No cardiac catheterization data or autopsy findings are available in this case which leaves some doubts as to whether aortic stenosis was the cause of death Reynolds and co workers[16] described one case with a normal electrocardiogram and sud den death in a 4 1/2 year old boy where the diag nosis of valvular aortic stenosis was confirmed by autopsy Glew and associates[13] also described a case of a 2 3/12 year old boy with severe aortic stenosis proved by autopsy who had died sud denly and had had a normal electrocardiogram. However, all had histories of syncopal attacks indicating the need for repeat catheterization From this we can surmise that sudden death with a normal electrocardiogram in aortic stenosis is possible but extremely rare considering how com mon an anomalous aortic stenosis is

Radiographic changes Radiographic findings of the chest do not correlate well with severity of the lesion according to Cohen and co workers[6] Friedman Modlinger and Morgan[3] in a group of nine patients found normal heart size and configuration in six patients with mild left ven tricular enlargement in three patients Poststen

otic dilation was present in all nine patients at the time of the second hemodynamic study though three cases did not demonstrate this prior to initial catheterization Cohen Friedman and Braunwald[6] noted poststenotic dilation in all 15 patients throughout the study period however their youngest patient was four years of age The heart size and contour were normal in 11 patients at the initial study four patients developed mild rounding and posterior displacement of the left ventricular silhouette Of the 19 patients reported by Hurwitz [9] mild cardiomegaly was noted in seven patients and dilation of the ascending aorta was noted in 14 patients These findings correlated poorly with severity of obstruction and did not progress significantly This is similar to our experience Since we found poststenotic dilation in only five of the 22 patients at the initial study and in 15 at the repeat study our impression is that this finding is an acquired manifestation related to duration of the obstruction

In our experience both valvular and subvalvular aortic stenosis may be progressive lesions in childhood, the subvalvular being more so than the valvular It is important to recognize that even mild hemodynamically unimportant lesions can subsequently become surgically important.

Summary

The present study is an attempt to clarify the natural history of valvular and subvalvular aortic stenosis Twenty eight patients with isolated and uncomplicated congenital aortic stenosis who had serial hemodynamic evaluation without intervening surgery were selected They were divided into three groups according to the severity of the peak systolic pressure gradient. At the initial study 16 of the 28 patients had mild stenosis 11 patients had moderate stenosis and one patient had severe stenosis On restudy there were only 9 patients with mild stenosis 12 patients with moderate stenosis and 7 patients with severe stenosis The cardiac index and right sided hemodynamics were normal The electrocardiographic and radiographic findings in relation to severity of the lesion were also observed. It is our feeling that both valvular and subvalvular aortic stenosis are progressive lesions the subvalvular being more so than the valvular

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Hemodynamic changes during ventricular pacing in patients with complete heart block and aortic and mitral valvular heart disease

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In patients with acquired complete heart block (CHB) not due to digitalis toxicity or surgery the incidence of accompanying valvular heart disease has been reported to be from 4 to 19 per cent [1-6] Both aortic and mitral valve disease appear to accompany CHB with similar frequency, the prevalence varying between series [1,4,8] Yet little data is available about either the effect of valvular heart disease on the hemodynamics of CHB or the hemodynamic response to ventricular pacing in patients with both CHB and valvular heart disease [7] Patients with untreated valvular heart disease and CHB have been thought to have a poorer prognosis than patients with CHB and normal valves [9] This may be due to the additive adverse effect of valvular heart disease on ventricular function which has been previously compromised by CHB

Increasing the heart rate from slow ventricular rates to normal in patients with CHB may lead to improvement in ventricular function which is greater than that which occurs when the heart rate is increased from normal to faster heart rates This improvement in ventricular function is usually manifested by a decrease in ventricular end diastolic filling pressure and volume and by an increase in contractility [9,10] In patients with CHB and valvular heart disease the improvement in ventricular function may be modified by the nature of the valvular disease

Symptoms resulting from valvular heart disease may also be modified by the onset of slow ventricular rates resulting from CHB Physical findings may be appreciably altered since as the ventricular rate is decreased stroke volume increases ejection periods change, and ventricular volume and pressures increase Since both CHB and valvular heart disease may independently lead to the onset of symptoms it seems reasonable that the superimposition of these two problems might lead to a striking increase in symptoms

Although several reports describe hemodynamic changes in patients with valvular heart disease when the rate is increased from normal,[11,12,24] there is little information when rates are increased from slow to normal levels The purpose of this study is to evaluate the acute hemodynamic response to an increase in ventricular rate by pacing from slow rates to more nearly normal levels in patients with CHB and valvular heart disease Particular reference is paid to changes in ventricular filling pressures and valvular gradients which may pertain to changes in symptoms and physical signs

Method and materials

Patient material There were 16 patients with CHB, with ventricular rates all less than 45 beats per minute None of the patients had recent myocardial infarction, or congenital or surgically acquired heart block Patients were divided into Groups A and B (Table I)

Group A consisted of six patients with CHB (mean heart rate 41 beats per minute) and valvu

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Table I Clinical data

Group	Age (yr)	Sex	BSA (M^2)	Atrial rhythm	Angina	Syncope	Dyspnea	Digitalis	NYHA	Valvular disease
A CHB and valvular heart disease										
1	68	F	1 40	AF	-	+	+	-	III	MS
2	60	M	1 73	NSR	-	-	-	-	II	AS
3	65	M	1 66	NSR	+	+	+	+	III	AS
4	55	M	1 81	NSR	-	-	+	+	II	AI
5	52	M	2 12	NSR	+	+	+	-	III	AI
6	57	M	1 58	NSR	-	-	+	-	II	AS and AI
B CHB without valvular heart disease										
1	50	F	1 41	NSR	-	+	-	-	II	
2	73	M	2 38	NSR	+	-	+	-	III	
3	72	F	1 86	NSR	-	-	+	-	II	
4	86	M	1 69	AF	-	-	+	+	III	
5	78	M	2 02	NSR	-	-	-	-	II	
6	51	M	1 81	AF	-	-	-	-	II	
7	70	F	1 83	AF	-	-	+	-	II	
8	80	M	1 80	NSR	-	-	-	-	II	
9	78	M	2 01	NSR	-	-	+	-	III	
10	68	M	1 87	NSR	-	+	+	-	III	

F female M = m le AF = atrial fibrillation NSR = normal s us rhythm + = present - = absent, MS = mitral tenosis AS = aortic stenosis AI = a t c n ffic ency and NYHA = New Y rk H rt Associ tion Funct onal Class ficat on

lar heart disease All patients were symptomatic however patient No 2 complained only of fa tigue

Group B consisted of 10 consecutive patients with CHB (mean heart rate 39 beats per minute) and no valvular heart disease Three of the ten patients complained solely of fatigue No patient was acutely digitalized during the study Partial data from patients Nos 4 and 5 have been published elsewhere [9,10]

Methods Right and left heart catheterization was performed in each patient A bipolar elec trode catheter was introduced through an an tecubital vein and the tip was positioned in the apex of the right ventricle (RV) Arterial cathe ters were positioned with the tips in the apex of the left ventricle (LV) and in the ascending aorta (Asc Ao) Central aortic catheters were u ed to eliminate peripheral pulse pressure augmenta tion and to more accurately delineate measured intervals The mid chest position from the angle of Louis was used as the zero reference level

The left atrial (LA) pressure was measured directly in three patients (Group A patients Nos 2 and 4 and one patient from Group B) and esti mated from the pulmonary artery wedge (PAW) pressure in 13 patients The left ventricular end diastolic (LVFD) pressure was measured in all pa tients

An oscilloscopic photographic recorder (Elec tronics for Medicine White Plains N Y) was used for recording pressures and dye curves Statham P23 Db strain gauge transducers were used. The catheter manometer recording system was shown to have a damped natural frequency response of 15 to 25 cycles per second ± 5 per cent. Cardiac output (CO) was determined by the dye dilution technique with the use of indo cyanine green (Cardio green dye Hynson, Westcott and Dunning Baltimore Md.) and a densitometer (Waters X 302 Rochester Minn) Electrical pacing was accomplished with an ex ternal pulse generator (Medtronic Minneapolis Minn) With the exception of patient No 3 who was initially paced at a rate of 48 beats per minute studies at the idioventricular rate (con trol) preceded studies done during pacing (study) A 20 minute interval for stabilization following the onset of pacing preceded any measurements

Left ventricular minute work index (LVMWI) in kilogram meters per square meter of body sur face area (Kg M /min /M^2 BSA) was calculated as the product of the cardiac indexes (L /min /M^2) and the planimeterized mean systolic aortic pressure (mm Hg) and 0 0144 Left ventricular stroke work index (LVSWI) in gram meters per beat per square meter of body surface area (g M /bt /M^2 BSA) was calculated as the product of

Table II (Group A) hemodynamic data in patients with CHB and valve disease

Patient No Diagnosis	1 MS	2 AS	3 AS	4 AI	5 AI	6 AI and AS
*Variable**						
Heart rate (bts /min)†	39	33	48	40	45	41
	66	76	91	80	75	81
Cardiac index (L /min /M ^{2})‡	2 6	2 1	1 6	2 4	3 3	2 1
	3 2	2 1	1 7	3 2	3 2	2 7
Stroke index (ml /bt /M ^{2})	67	65	33	60	74	51
	49	28	19	39	42	34
Pressures (mm Hg)						
PAW	24	14§	20	28§	26	27
	27	9	—	7	16	24
LVEDP	20	15	26	25	30	37
	12	6	8	5	13	18
PA (mean)	28	21	30	36	30	32
	34	18	16	18	26	32
LV systolic		179	158			270
		166	134			286
Asc Ao systolic	168	150	114	205	165	220
	161	140	100	135	170	244
Asc Ao Diastolic	57	60	45	51	40	60
	71	78	61	66	50	74
Asc Ao mean	92	85	66	87	82	95
	101	96	75	93	96	100
Ejection per beat (sec)	37	39	40	44	45	42
	31	29	31	32	39	31
Ejection per minute (sec)	14 4	12 9	19 0	17 4	20 3	17 2
	20 5	22 0	27 8	25 2	29 3	25 1
LVSWI (G M /bt /M ^{2})	137 44	143 6	57 72	122 7	133 2	110.2
	92 86	57 9	29 18	65 7	74	71 5
LVMWI (Kg M /min /M ^{2})	5 33	4 8	2 80	4 9	5 9	4 45
	6 06	4 4	2 61	5 4	5 6	5 7
TTI per minute (mm Hg sec)	2056	1480	2303	2499	2538	2583
	2693	2491	2960	2995	3583	3666
TTI per beat	52 7	45 0	48 0	62 5	56 3	63 0
	40 8	32 7	32 5	37 4	47 7	45 3

*See text for abbreviations
†Two lines of data follow each variable The top line indicates data obtained during control and the bottom line during study conditions
‡Reflects net forward flow and does not include regurgitant flow in patients with aortic insufficiency
§Left atrial pressure measured directly

the stroke index, and the mean systolic aortic pressure and 0 0144 The tension time index (TTI) was computed as the product of the mean systolic aortic pressure and the ejection time per beat or the ejection time per minute and was expressed as millimeters of Hg seconds per beat or millimeters of Hg seconds per minute respectively [13] In patients with aortic stenosis (Patients Nos 2 and 3) the mean systolic left ventricular pressure was used in place of the mean systolic aortic pressure in the calculation of ventricular work and the TTI Resistances were calculated as the quotient of the mean pressure and the cardiac output and expressed as dynes sec cm $^{-5}$

With the exception of patient No 1, angiography was done on all patients in Group A Ascending aortography in patient No 5 demonstrated regurgitation of contrast material into an enlarged left ventricle such that the left ventricular cavity was better opacified than the ascending aorta (4+ on a −0 to 4+ scale) In patients Nos 4 and 6 there was regurgitation of enough contrast material to outline the left ventricle (2+ aortic insufficiency) but less well than the aorta Single plane cineangiography in the right anterior oblique position was used to determine changes in ventricular dimensions at control and during study conditions in patient No 4 After

Table III (Group B) hemodynamic data in patients with CHB and normal cardiac valves

Variable	*Control* Mean ± S.D	*Study* Mean ± S.D	*P value* Control to Study
Heart rate (bt /min.)	38 7 ± 5 4	77 6 ± 5.5	<0 001
CI	2 2 ± 0 6	2 6 ± 1 0	<0 02
SI	56 7 ± 18 6	34 7 ± 9 9	<0 001
PAW (mm Hg)	13 3 ± 3 9	10 7 ± 3 1	<0 050
LVEDP (mm Hg)	14 1 ± 3 5	9 7 ± 2 6	<0 005
PA m (mm Hg)	20 8 ± 4 0	21 7 ± 6 8	<0 5
Ao S (mm. Hg)	161 ± 29	149 ± 3	<0.2
Ao D (mm Hg)	66 ± 16	88 ± 19	<0 001
Ao m (mm Hg)	92 ± 15	97 ± 18	<0 2
RA (mm Hg)	7 8 ± 0 6	5 3 ± 1 6	<0 001
Ejection per beat (sec)	0 37 ± 0 04	0 28 ± 0 04	<0 001
Ejection per minute (sec)	14 0 ± 1 5	20 7 ± 2 3	<0 001
LVSWI (G M /bt./M ^{2})	104 0 ± 47 0	58 6 ± 25 5	<0 005
LVMWI (Kg M /min./M ^{2})	4 2 ± 1 7	4 4 ± 2 1	<0.500
TTI per minute (mm Hg per sec)	1 832 ± 444	2 515 ± 521	<0 001
TTI per beat (mm Hg per sec)	46 0 ± 10 4	32 0 ± 5 1	<0 005

See text for abbreviations

correction for x ray distortion the left ventricular volume was estimated by the method of Greene and co workers[14] Left ventriculography in patients Nos 2 and 3 and aortography in patient No 5 failed to demonstrate significant mitral insufficiency

The mitral valve area (MVA) and the aortic valve area (AVA) were calculated by the method of Gorlin and Gorlin[15] with the systolic ejection period (SEP) and a diastolic filling period (DFP) being determined from central aortic pressure tracings The mean diastolic gradient (MDG) across the mitral valve was determined as the difference between the mean PAW pressure and the measured mean left ventricular filling pressure The MDG across the mitral valve was also determined by planimetry but this method was not used for calculating MVA[16,17] The aortic systolic gradient was determined by integrating the area between the left ventricular and aortic pressure curve with a polar planimeter

Patients with sinus atrial mechanism and CHB have fluctuating ventricular mechanics dependent upon the relation of atrial contraction to the onset of ventricular systole[10,18] Care was taken to adequately sample in those patients with sinus atrial mechanism

Results

Individual hemodynamic results of Group A are presented in Table II and mean values and standard deviations of Group B are presented in Table III In patients with CHB and normal cardiac valves (Group B) there were significant increases in the cardiac index ejection time per minute and the TTI per minute when the ventricular rate was increased by pacing Concomitantly there were significant decreases in the stroke volume stroke work ejection time per beat and TTI per beat from the control to the study conditions In addition there were significant decreases in the mean pressure in the left atrium the LVED pressure and a significant increase in the aortic diastolic pressure when the heart rate was increased by pacing There were no significant changes in the mean pressure in the pulmonary artery (PA) or aorta the systolic pressure in the aorta the LVMWI the peak derivative of the left ventricular pressure and the systemic or pulmonary vascular resistance

In patients with CHB and no valvular heart disease (Table III) there was a small but significant increase in cardiac index in association with pacemaker induced doubling of the heart rate In contrast (Table II) patients with pure aortic stenosis (AS) exhibited no increase in CI nor did one of the two patients with aortic insufficiency (AI)

The LVEDP decreased in all patients in Group A (mean decrease 15 2 mm Hg) to a greater extent than the mean LVEDP decreased in patients in Group B (4 4 mm Hg) This decrease in

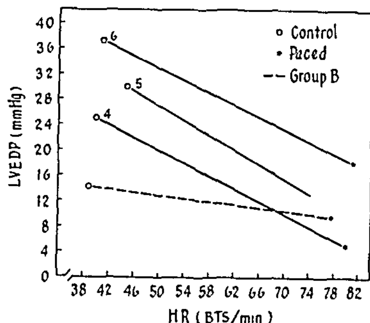


Fig 1 LVEDP at the control and study rates in the three patients with AI compared with control Group B

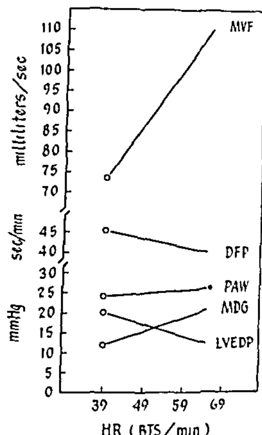


Fig 2 Changes in mitral valve flow (MVF) diastolic filling period (DFP) pulmonary artery wedge pressure (PAW) the *mean diastolic gradient (MDG) and the left ventricular end* diastolic pressure are indicated as the heart rate is increased from 39 to 69 beats per minute

LVEDP was most striking in patients Nos 4 through 6 who had aortic insufficiency and who had much higher ventricular filling pressures than the mean control values in Group B (Fig 1) A large decrease in LVEDP was also noted in patients with aortic and mitral stenosis With the exception of patient No 1 the PAW and LA pressure usually mirrored changes in the LVEDP In patient No 1, (MS) mitral valve flow (MVF) *increased strikingly during pacing* (112 c c per second) over the control value (74 c c per second) although the cardiac index was only modestly increased and the stroke index fell The increase in MVF (milliliters per second) across the fixed resistance resulted in an increase in the MDG Although the MDG nearly doubled from the control value (13 to 22 mm Hg) when the ventricular rate increased the mean LA pressure increased by only 3 mm Hg due to a decrease in the LVEDP (Fig 2) There was no end diastolic gradient across the mitral valve at the slow idioventricular rate, but an end diastolic gradient appeared when the heart rate was increased and the diastolic filling period shortened (Fig 3) The mitral valve area was calculated to be 0 71 cm² at the control rate and 0 77 cm² during pacing *In spite of the elevated LVEDP*, patient No 1 had the highest stroke index in the series when the heart rate was in the physiologic range

In patient No 4 (AI) the end diastolic volume (EDV) decreased from a control value of 280 ml *to a study value of 205 ml* when the ventricular rate was increased The regurgitant volume per *beat decreased from* 139 *to* 109 *ml* per beat while the regurgitant flow increased from 5 6 to 8 7 L per minute when the heart rate was increased

There was a 13 mm Hg decrease in the peak left ventricular systolic pressure and a 13 mm reduction in the mean systolic gradient from the idioventricular to the paced rhythm in patient No 2 (AS) LVSWI decreased by 60 per cent when the ventricular rate was increased toward more nearly normal values The mean systolic gradient was influenced by the timing of the atrial contraction as has been previously[16] described

Patient No 3 (AS) was studied at paced resting rates *of 48 70, 91 125 and 150 beats per minute* and in addition at 70 beats per minute during *supine leg exercise* As the heart rate increased and the stroke volume fell the mean systolic gradient decreased (Fig 4) The stroke volume correlated well with the mean systolic gradient (r = 0 94) and the calculated valve area changed very little (0 39 to 0 50 cm² at rest and 0 63 cm²

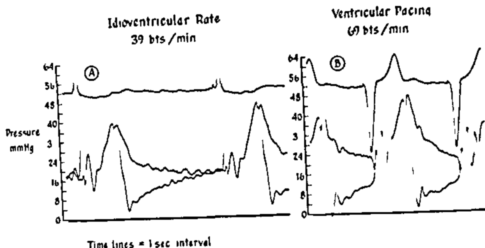


Fig 3 Left ventricular and pulmonary artery wedge pressure tracing in patient No 1 with mitral stenosis. The decrease in LVEDP and increase in MDG as the heart rate is increased (A to B) is apparent.

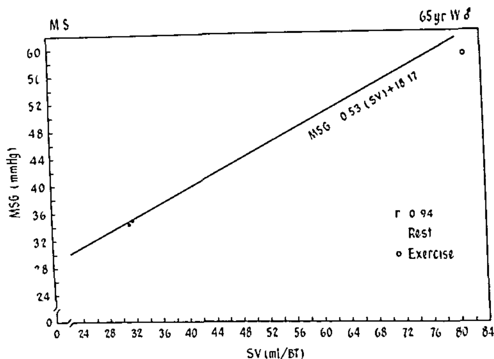


Fig 4 Relationship between stroke volume and mean systolic gradient (MSG) in patient No 2 with aortic stenosis

during exercise) LVSWI decreased by 50 per cent when the ventricular rate was increased from 48 to 91 beats per minute Patients Nos 2 and 3 (both AS) had heavily calcified aortic valves In patient No 3 calcification extended from the aortic valve into the ventricular septum. Coronary arteriography in patient No 3 excluded significant coronary artery disease

Discussion

As the ventricular rate is increased from slow to more nearly normal levels in patients with CHB improvement in ventricular function may be demonstrated as a decrease in left ventricular end diastolic filling pressure and volume and by an increase in contractility[9,10] This change in ventricular function may be more marked in pa

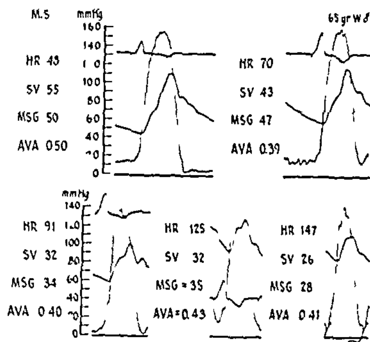


Fig 5 Left ventricular and aortic pressure in patient No 2 with aortic stenosis As the heart rate increased and stroke volume falls the mean systolic gradient (MSG) decreases

tients who have had to compensate for both CHB and for valvular heart disease Patients with aortic valvular disease had greater reductions in LVEDP than that found in patients with CHB alone (Group B) the most marked improvement occurred in patients with CHB and aortic insufficiency

Patient No 1 was unusual in that LVEDP was elevated in spite of the presence of mitral stenosis and in the absence of clinical evidence of mitral insufficiency [7] The prominent V wave (Fig 3) likely represented left ventricular failure and is secondary to the elevated filling pressure but also suggests the possibility of undetected mitral insufficiency In patients with mitral stenosis and left ventricular failure the rate of ventricular filling is influenced both by the resistance at the mitral valve and by the compliance of the left ventricle In patient No 1 with mitral stenosis mitral valve flow increased strikingly from the control to study condition resulting from an increase in cardiac output and a decrease in the diastolic filling time In spite of a 70 per cent increase in the MDG there was only a modest rise in the left atrial pressure during ventricular pacing due to a significant reduction in the ventricular filling pressure (Fig 2)

This reduction in LVEDP may, in part, be due to a reduction in ventricular volume a known effect of pacing, even though the resistance across the mitral valve remained constant Perhaps a more important factor in reducing the ventricular filling pressure was the positive inotropic effect of increasing the heart rate from slow to more normal levels [9,10] Similar results have been reported in another patient with a comparable degree of mitral stenosis and CHB[7] and during atrial pacing in patients with mitral stenosis and sinus rhythm [11] However, in that patient[7] the LVEDP was normal at the slow ventricular rate and decreased still further as the heart rate was increased to more nearly normal levels As the heart rate was increased from a rate of 60 beats per minute to a rate of 120 beats per minute, the mean diastolic gradients increased solely as a result of an increase in left atrial pressure since the LVEDP did not fall further Thus by increasing the heart rate from slow to normal in patients with tight mitral stenosis there is a slight rise in left atrial pressure associated with a fall in ventricular filling pressures which may be especially beneficial if left ventricular failure is present. However further increasing the heart rate may further increase the left atrial pressures and produce the onset or aggravation of symptoms This suggests that patients who have mitral stenosis, CHB and left ventricular dysfunction may experience greater clinical improvement during pacing than similar patients with a normally functioning left ventricle

Although the cardiac index changed little in patients with aortic insufficiency when the ventricular rate was increased by pacing there was a striking reduction in the LVED pressure The decrease in LVED pressure from the control value to a study value was three times that of the mean decrease in LVEDP of patients in Group B (Fig 1) Assuming that ventricular compliance did not change the decrease in LVED pressure in the patients with aortic insufficiency likely results from a decrease in ventricular volume which in turn results from a decrease in diastolic filling time with pacing, thereby reducing the time available for aortic regurgitation per beat. In patient No 4 there was a reduction in the regurgitation per beat while the regurgitation flow per minute increased This likely results from a decrease in the total time per minute available for regurgitation even though most of the regurgitation occurs early in diastole when

the aortic left ventricular gradient is greatest In a report of eight patients with aortic insufficiency who were studied while in sinus rhythm a significant reduction in LVEDP and a reduction in regurgitant volume per beat was obtained with an increase in mean heart rate from 70 to 104 beats per minute [24] The rate of regurgitation however did not change consistently in that study while the mean DFP decreased by 7 per cent from 36 6 to 33 9 sec per minute In patients with aortic insufficiency and CHB reported here the reduction in DFP ranged from 18 to 27 per cent or from 7 5 to 9 0 sec per minute

During tachycardia induced by exercise in patients with aortic stenosis there is little change or a slight increase in the mean systolic gradient as heart rate and aortic valve flow increases although results have been variably reported.[20 23] Variable results in turn may be due to the use of peripheral arterial pressures for estimating gradients and including some patients with aortic insufficiency [23] During ventricular pacing in patients Nos 2 and 3 however there were decreases in the stroke volume systolic aortic valve flow and the mean systolic gradient (Fig 5) In patient No 3 the mean systolic gradient correlated well with stroke volume during exercise and at various paced rates (r = 0 94) (Fig 4) A slight increase in the exercising calculated AVA over that calculated at rest has been noted[20 21] and may be due to changes in the geometry of the valve during exercise and/or to changes in the estimation of the components of the Gorlin formula Central aortic catheters minimize the effect of pulse wave distortion during exercise and, therefore lead to a more accurate estimation of the mean gradient [20]

The incidence of CHB in patients with aortic stenosis has been estimated at less than 1 per cent.[19] Since the onset of both aortic stenosis and CHB may be heralded by syncope or left ventricular failure an accurate assessment of the degree of aortic stenosis is essential.[19] Syncope is the first manifestation of CHB in about 20 per cent of the cases [4] The characteristically slow rising pulse and systolic murmur in patients with aortic stenosis may be modified by the increase in stroke volume when the ventricular rate is slow and clinical estimates of severity of valvular stenosis may be misleading

The deleterious effect of CHB superimposed on valvular heart disease is strikingly demonstrated in patients with bacterial endocarditis When patients with bacterial endocarditis superimposed on aortic valvular disease develop CHB the mortality is strikingly increased over patients who remain in sinus rhythm.[25] In such patients increasing the ventricular rate by pacing may lead to striking clinical improvement allowing time for adequate antibiotic therapy and, if necessary an orderly approach to valve replacement

Dyspnea is present in about 40 per cent of patients with complete heart block in a large series[7] and was present in 60 per cent of the cases reported here Reduction in the LVED and LA pressure could well account for the relief of dyspnea so frequently volunteered by patients with CHB when the ventricular rate is increased by pacing

Thus increasing the ventricular rate in patients with complete heart block and valvular heart disease results in hemodynamic changes dependent, in part on the type of valvular disease present. When the heart rate is increased by pacing the mean diastolic gradient in the reported patients with mitral stenosis is increased[7] while the systolic gradient in patients with aortic stenosis is decreased In patients with elevated filling pressure and elevated end diastolic volume of the left ventricle there may be a return toward more normal values as in patients with aortic insufficiency

Summary

Increasing the heart rate to near normal in patients with complete heart block (CHB) and slow ventricular rates may lead to greater improvement in ventricular function than when the heart rate is increased from normal to more rapid heart rates. Improvement in ventricular function is usually manifested by a decrease in left ventricular end diastolic pressure (LVEDP) and volume and by an increase in contractility In patients with both CHB and valvular heart disease improvement in ventricular function during pacing may be modified by the nature of the valvular disease

Hemodynamic data from six patients with both valvular heart disease and CHB were compared with those from ten patients with CHB and normal cardiac valves Hemodynamic studies were performed at slow or idioventricular rates and again after increasing the heart rate to more nearly normal levels by ventricular pacing

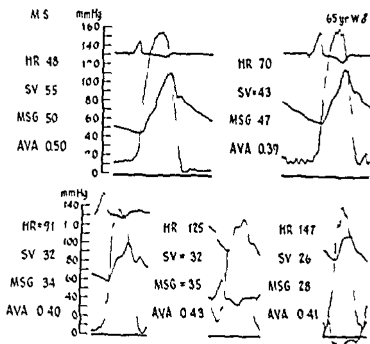


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Preclinical abnormality of left ventricular function in diabetes mellitus

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Cardiac disease would appear to be an important cause of mortality in diabetes mellitus [1,2] Although accelerated atherosclerosis of the coronary arteries has previously been considered the major pathogenetic factor more recent postmortem studies have questioned the significance of coronary disease as accounting for premature death in adult onset diabetes Two separate studies found no greater degree of obstructive disease of the coronary arteries in diabetics compared to normal control subjects [3,4]

Since extravascular complications of diabetes have been described in other organs [5] this study was undertaken to investigate the status of ventricular function as a measure of potential myocardial involvement in patients with diabetes mellitus By excluding subjects with clinical evidence of heart disease or complications such as hypertension or obesity which may independently affect the myocardium [6,7] the question of a preclinical form of cardiac abnormality in the diabetic subject analogous to that described in chronic alcoholism was approached [8,9] Noninvasive measurement of the systolic time intervals has made this study feasible since these provide a reasonable correlation with more direct measures of cardiac performance in the absence of complicating lesions such as valvular or pulmonary vascular disease [10,11]

Materials and methods

The function of the left ventricular myocardium was evaluated in 25 diabetic subjects ranging in age from 20 to 56 years there were 15 males and 10 females None had evidence of other systemic diseases which might potentially affect the heart Subjects were selected who were ambulatory clinic patients or who were at least one week postrecovery from an episode of ketoacidosis that required hospitalization None of the subjects had cardiorespiratory symptoms at any time or any clinical electrocardiographic or x ray evidence of cardiac abnormality In addition individuals were excluded if they were more than 15 per cent above ideal weight had an arterial pressure above 140/90 or presented clinical evidence of renal retinal or neurologic complications Each diabetic subject was carefully interviewed to exclude from the study subjects with an established or probable history of chronic alcoholism or those with a cigarette smoking history greater than one pack per day

Diabetes was known to be present from one month to 25 years Seven subjects were new diabetic patients and were not receiving hypoglycemic agents Eight subjects were on oral hypoglycemic agents and ten subjects received insulin While none of the subjects had symptoms suggestive of angina subjects above 40 years of age had a double Master s stress test all of the subjects were found to have normal responses with ST depression never exceeding 1 0 mm The fasting blood sugar on the morning of study was between 126 and 240 mg per cent Serum elec

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When obstruction to left ventricular inflow (mitral stenosis) co existed with CHB increasing the heart rate resulted in a reduction of an elevated LVEDP to normal This resulted in only a small increase in left atrial pressure in spite of a striking increase in the mean left atrial ventricular gradient

When obstruction to left ventricular outflow prevailed (aortic stenosis) improvement in cardiac function was manifested mainly by a decrease in LVEDP and was accompanied by a decrease in left ventricular stroke work When a large regurgitant volume (aortic insufficiency) was added to a ventricle which has enlarged subsequent to CHB there was striking elevation in ventricular filling pressures which returned to more nearly normal levels when the heart rate was increased This was accompanied by a reduction in regurgitant stroke volume in the patient in whom it was measured

Thus an increase in heart rate may be especially beneficial to those patients with CHB who also have valvular lesions which contribute to an increase in LVEDP and end diastolic volume Careful hemodynamic evaluation is helpful in determining appropriate therapy in these patients

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Table I Results in control and diabetic subjects

Group	Blood sugar (mg %)	Heart rate	Blood pressure (mm. Hg) S	Blood pressure (mm. Hg) D	QS_2	LVET	PEP	PEP/LVET	CT	IVT
Normal subjects (N = 37)	98	72	121	78	368	287	81	0.284	4[illegible]	37
S E M ±	[illegible]7	1 6	2 2	1 2	4	3	2.2	0 008	2	2 1
Diabetics (N = 25)	200	78	122	83	369	260	108	0 424	52	56
S E M ±	14	2.5	3	1 0	8	7	3	0 019	2.3	2 2
P vs normal subjects	<0 001	<0 02	N.S	<0 01	N.S	<0 001	<0 001	<0 001	<0 02	<0 001

Abbreviations QS_2 total electromech nical systole in milliseconds LVET left ventricular ejection time in milliseconds PEP pre-ejection period in mill seconds CT conduction time in milliseconds ($Q\text{-}S_1$) and IVT isovolumic contraction time in milliseconds.

Table II Diabetics on dietary management alone

Subjects	Sex	Age	Duration (years)	Blood sugar (mg %)	Heart rate	Blood pressure (mm. Hg) S	Blood pressure (mm. Hg) D	QS_2	LVET	PEP	PEP/LVET	CT	IVT
1	M	46	0 67	172	83	128	88	366	260	106	0 407	46	60
2	F	50	2	99	68	120	88	380	268	112	0 417	65	47
3	M	48	0 08	230	66	105	80	369	256	113	0 441	48	6[illegible]
4	M	43	0 08	162	81	116	84	346	258	88	0.341	64	34
5	M	41	0 08	150	88	110	78	359	240	119	0 495	53	66
6	F	44	1	150	62	130	80	413	303	110	0 363	40	70
7	M	37	1	180	55	110	76	418	310	108	0 348	64	44
Mean		44	0 7	163	72	117	82	379	271	108	0 402	53	55
S E M ±		1 7	0 27	1[illegible]	4 6	3 6	1 7	10	10	3 7	0 021	3 5	5 1
P vs normal subjects		<0 01		<0 001	NS	NS	NS	NS	NS	<0 001	<0 001	<0 05	<0 001

Units fo systol c t me intervals are in mill se ond abbreviations as in Table I

glycemic agents there was a significantly shorter LVET PEP and IVT were prolonged and the calculated ratio was almost 50 per cent greater than in the control subjects Aortic diastolic pressure was above the level of the normal sub jects although still within the normotensive range The insulin treated group had a similar degree of PEP and IVT prolongation as well as an increment in the PEP/LVET ratio The shorten ing of LVET was greater in this group and the heart rate and arterial diastolic pressure were higher than in normal subjects but within the normal range There was a small but significant prolongation of CT in the patients managed by diet alone or oral hypoglycemic agents, but not in the insulin treated group

Since there was no significant difference in the PEP/LVET ratio in the three diabetic subgroups we have compared the influence of age in the pooled diabetic patients There was no significant difference between normal subjects from the third through the fifth decade nor did the difference between diabetic and normal subjects alter with age Diabetic subjects in the third decade had a PEP/LVET ratio of 0 41 ± 0 03 compared to 0 292 ± 0 01 in normal subjects of the same age group In the fifth decade diabetic subjects were 0 445 ± 0 03 versus 0 313 ± 0 01 in normal subjects When the diabetic subjects were pooled by sex the males were not signifi cantly different from the females 0 441 ± 0 027 (N=14) in the former versus 0 394 ± 0 021 (N=11) The normal subjects showed no sex difference

Discussion

The use of the systolic time intervals has served as a useful noninvasive measure of left

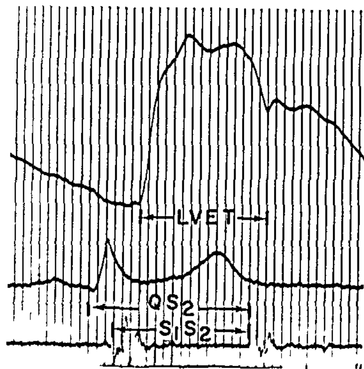


Fig 1 Simultaneous recording of electrocardiogram (Lead II) phonocardiogram and carotid pulse tracing at paper speed of 200 mm per second with time markers at 0 02 sec The variables measured directly are QS_2 S_1S_2 and LVET (abbreviations and definitions under Methods) as shown From these CT PEP and IVT are obtained by calculation

trolytes total protein albumin and blood urea nitrogen (BUN) as well as the hematocrit and white cell count were within normal limits in each patient Thirty seven subjects between 23 and 46 years of age (21 males and 16 females) who had no history of diabetes in themselves or in their families served as control subjects

The systolic time intervals (STI) were obtained at least two hours postprandial in mid morning hours using the method and instrumentation described by Weissler Harris and Schoenfeld[12] from simultaneous electrocardiograms and carotid pulse tracings Recordings were made on an oscillographic recorder (Electronics for Medicine White Plains N Y) at a paper speed of 150 to 200 mm per second with time markers at 0 02 sec (Fig 1) Fifteen to 20 complexes were analyzed and averaged The measurements were calculated without the investigator knowing the identity of the subject studied

Total electromechanical systole (QS_2) left ventricular ejection time (LVET) and the duration of mechanical systole (S_1S_2) were measured directly The QS_2 was measured from the beginning of the Q wave in Lead II to the first rapid deflection of the second heart sound LVET was measured from the onset of the rapid upstroke of the carotid pulse to the nadir of the dicrotic notch The pre ejection period (PEP) the PEP/LVET ratio and the isovolumic contraction time (IVT) were derived from the direct measurements PEP was calculated as the difference between QS_2 and LVET and was not rate corrected since no significant relation of PEP to heart rate has been found in recent investigations LVET was corrected for heart rate by a regression equation [13]

IVT was calculated as the difference between S_1S_2 and LVET The QS_1 interval or conduction time (CT) was derived from the difference between PEP and IVT Our previous study[11] in which STI were correlated with several invasive measures of myocardial contractility demonstrated that augmented contractility is associated with decreases in PEP, IVT and PEP/LVET and depression of contractility with increases in these variables Complicating valvular lesions septal defects, or pulmonary vascular disease distorted the STI [11]

Heart rate was obtained by multiplying 60 by the reciprocal of the mean R R interval for the 15 or 20 complexes Blood pressure was measured by sphygmomanometry with diastolic pressure taken as the muffling of Korotkov sounds Statistical analyses were performed using conventional methods for small samples Differences between groups were evaluated by the t test

Results

Table I summarizes the results in diabetic and normal control subjects Diabetic subjects had slightly higher levels of heart rate and arterial diastolic pressure that were significantly different from normal subjects The abnormalities of STI in the diabetic subjects included a shorter LVET that was also significantly shortened when corrected for heart rate ($P < 0.001$) PEP was prolonged and the ratio of PEP to LVET was substantially increased Both CT and IVT were of greater duration, while QS_2 and S_1S_2 were of similar duration as in the normal subjects

These diabetic subjects were subdivided according to mode of therapy and the individual data are presented in Tables II IV Patients managed on diet alone demonstrated a PEP PEP/LVET and IVT that were significantly higher than in the control subjects while the heart rate diastolic pressure and LVET were similar to values in the normal control subjects

In the subgroup treated with oral hypo

were slightly higher in the total diabetic group these elevations appeared to be insufficient to affect the STI Consistent with this interpretation is the fact that the diabetic subgroup on dietary management had an elevated PEP/LVET ratio at heart rate and aortic pressure levels similar to control subjects

Although a longer pre ejection period and a shorter ventricular ejection time is characteristic of the failing heart [11,14] the moderate abnormalities of these parameters in the diabetic patients may not be exclusively related to an abnormality of myocardial contractility Reduction of venous return in normal subjects results in qualitatively similar changes in these time intervals [15]

That altered preload may at least contribute if not constitute the major determinant of this preclinical abnormality is suggested by data from an animal model [16] In dogs with alloxan diabetes for one year and in spontaneous diabetic animals diminished distensibility of the left ventricle was demonstrated without hypertrophy or decompensation During increased preload, the diabetic animals developed a significantly higher end diastolic pressure than normal controls with similar end diastolic volume increments With moderately enhanced afterload the diabetic animals failed to increase end diastolic volume as did the normal control animals

Since the altered distensibility was demonstrated only with acute interventions in the animal studies the abnormalities at rest in diabetic patients may not be entirely analogous However with the longer disease duration in the human subjects distensibility may be diminished to a greater extent and be sufficient to secondarily affect intrinsic contractility Alternatively diabetes may ultimately affect the contractile mechanism in a direct manner The only morphologic abnormality in the animal model consisted of accumulation of periodic acid Schiff (PAS) staining material in the interstitium while electron micrographs revealed no abnormalities of cell structure [16] PAS positive glycoprotein has also been observed in the myocardium of human diabetic subjects [17,18] so that the preclinical functional abnormality may be related to increased stiffness as a consequence of the altered interstitium

The recent study of Vihert Zhdanov and Matova[3] supports the position that diabetic subjects may not have more obstructive disease of the extramural coronary vessels than the general population In addition studies of the intramural vessels indicated that histochemical alterations may be present without compromise of the arterial lumen [4] The characteristics of the patients selected for study makes it improbable that clinically significant obstructive disease of the major coronary arteries was prevalent in this group as they were entirely without cardiovascular symptoms or signs The fact that the STI were substantially abnormal in the younger age diabetic subjects presumed to have less probability of large vessel disease is also supportive Exercise tests in the diabetic subjects over 40 years of age using multiple leads were uniformly negative It is noteworthy that patients with angina pectoris and significantly narrowed coronary arteries on angiogram have been reported to have less than a 23 per cent incidence of false negatives using the criterion of ST segment depression greater than 1 0 mm [19] Assuming that the proportion of false negatives is not greater in diabetic subjects without clinical evidence of heart disease myocardial ischemia would appear to be improbable as a basis for the preclinical abnormality Relevant to this question is the observation that patients with classic angina pectoris without cardiac decompensation may have normal systolic time intervals at rest [20]

The extent of the abnormal cardiac function was not correlated with fasting blood sugar levels or the sex of the patient Neither did duration of diabetes appear to be a determining factor although larger numbers and a more precise means of dating the onset of diabetes would be required for a firm conclusion as to the interrelationship of age and disease duration Whether the observed functional abnormality may progress to clinical heart failure may depend on intensification of the underlying pathophysiology in the myocardium or the superimposition of complications such as hypertension obesity or obstructive disease of the coronary vessels

Summary

Abnormal cardiac muscle function has been reported in experimental diabetes mellitus from this laboratory To examine left ventricular performance in diabetic patients without clinical evidence of myocardial ischemia or other cardiovascular disease a noninvasive measurement of

Table III Results in patients on oral hypoglycemic agents

	Subjects		Duration (years)	Blood sugar (mg%)	Heart rate	Blood pressure (mm Hg)							
	Sex	Age				S	D	QS_2	LVET	PEP	PEP/LVET	CT	IVT
1	M	51	15	176	64	118	80	420	300	120	0 4	59	61
2	F	52	1	216	92	100	82	369	251	118	0 47	52	66
3	F	29	1	219	92	140	90	360	260	100	0 384	40	60
4	M	53	4	180	82	130	80	328	215	113	0 525	64	49
5	M	53	6	160	66	160	88	404	293	111	0 378	46	65
6	F	48	4	150	70	114	78	413	305	108	0 354	54	54
7	M	49	0 5	389	83	120	88	339	214	125	0 584	60	65
8	M	66	0 19	310	63	110	76	387	280	107	0 382	66	41
Mean		48 9	4	225	77	124	83	378	265	113	0 435	55	58
SEM ±		3 0	1 7	29	4 3	6 7	1 8	12	13	3	0 029	3 2	3 2
P vs normal subjects		<0 01		<0 001	NS	NS	<0 05	N.S	<0 01	<0 001	<0 001	<0 05	<0 001

Units for systolic time intervals are in milliseconds abbreviations as in Table I

Table IV Results in diabetic subjects on insulin therapy

	Subjects		Duration (years)	Blood sugar (mg %)	Heart rate	Blood pressure (mm. Hg)							
	Sex	Age				S	D	QS_2	LVET	PEP	PEP/LVET	CT	IVT
1	F	20	9	200	102	115	80	318	211	107	0 507	40	67
2	M	41	4	245	88	115	78	305	188	117	0 622	57	60
3	M	39	3	245	90	126	88	330	205	125	0 609	65	60
4	F	34	2	180	61	120	80	398	299	99	0 331	54	45
5	M	31	2	136	88	118	80	311	230	81	0 352	32	49
6	M	32	3	145	87	115	75	319	240	79	0 329	35	44
7	F	28	4	130	79	120	88	369	292	77	0 263	30	47
8	M	51	25	160	66	120	78	456	306	150	0 49	72	78
9	F	39	2	265	92	140	90	365	250	115	0 46	51	64
10	F	45	5	350	73	150	88	375	276	99	0 359	41	48
Mean		36	5 9	206	83	123	84	355	250	105	0 432	48	56
SEM ±		2 8	2 2	22	4	3 7	1 7	15	13	7 2	0 039	4 5	3 6
P vs normal subjects		<0 05	–	<0 001	<0 01	NS	<0 05	NS	<0 001	<0 001	<0 001	NS	<0 001

Units for systolic time intervals are in milliseconds abbreviations as in Table I

ventricular performance in man The technique is not readily applicable in the presence of valvular disease particularly aortic stenosis However diffuse abnormalities of the left ventricle do show abnormal time intervals which correlate well with abnormalities of ejection fraction measured by angiography[10] or indicator dilution [11] Abnormalities of the left ventricular STI in diabetic patients may be considered to be a preclinical manifestation of cardiac malfunction and would appear to be analogous to the preclinical abnormality demonstrated in individuals with chronic alcoholism [8,9] An elevated PEP/LVET ratio is characteristic of the heart in failure by clinical criteria [11-14] but this approximates a twofold increment above controls as compared to the 40 per cent prolongation in these diabetic subjects *without clinical evidence of heart disease* Thus the abnormality of the systolic time intervals is intermediate between normal and that observed in cardiac decompensation

While heart rate and aortic diastolic pressure

Determination of zero reference level for left atrial pressure by echocardiography

P A N Chandraratna MD MRCP
With the technical assistance of
D Gindlesperger
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The mean left atrial pressure reflects the left ventricular filling pressure which is an important determinant of left ventricular performance Elevation of the left atrial pressure results in pulmonary venous congestion and ultimately pulmonary edema ensues Thus, accurate left atrial pressure measurements are of great import in the management of left ventricular dysfunction especially in the setting of acute myocardial infarction

An accurate zero reference level is a prerequisite for the reliable determination of intracardiac pressures Previous workers have used several different zero reference levels for hemodynamic measurements Five centimeters from the sternal angle the mid chest position and 10 cm from the back level have all been employed as zero reference systems in the past[1,2] The purpose of this study is to compare the chest wall to mid left atrium distance as assessed by echocardiography with the three zero reference levels mentioned above and to indicate the errors that may result from using such arbitrary reference systems

Materials and methods

The group studied consisted of 29 males and 21 females whose ages ranged from 17 to 70 years with a mean age of 48 Seventeen patients had valvular heart disease 15 patients had atherosclerotic heart disease 16 patients had no demonstrable heart disease and there was one patient with cardiomyopathy and one with hypertension Most of these patients were studied during their hospitalization for cardiac catheterization None had cardiac malposition or chest deformity Echocardiography was performed with the patient in a supine position An Ekoline 20 echocardiograph and E for M DR8 recorder were used A 2 25 MHz. 10 cm focus transducer was placed in the third or fourth interspace at the left sternal edge and angulated posteriorly medially and slightly upward until the two walls of the aorta were seen and aortic cusp echoes were visualized Another echo has been shown to arise from the posterior wall of the left atrium[3] The maximum left atrial dimension at the end of ventricular systole was obtained and the chest wall to mid left atrium distance (D) measured (Fig 1) Using a pair of calipers the antero posterior diameter of the chest (L) was measured at the level of the sternal angle with the patient in a supine position The first system (ZRL (1)) using a constant distance of 5 cm from the sternal angle for the zero level (Fig 2) The second zero reference level (ZRL (2)) is 10 cm from the back or (L−10) cm from the front of the chest (Fig 2) Mid chest or L/2 cm from the front of the chest is employed for the third system (ZRL (3)) (Fig 2) Since the ultrasound measurements were made from the third or fourth interspace the anterior posterior (AP) diameter of the chest at this level was also noted The difference 'between this distance and the corresponding value at the sternal angle was 1 cm or less in 48 patients The difference was 2 4 cm and 2 cm respectively in the other two patients Thus the corrected value for chest wall to mid left atrium distance in rela

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the systolic time intervals was carried out Simultaneous recordings of the electrocardiogram, heart sounds and carotid pulse were made in 25 diabetic subjects 20 to 56 years of age, and compared with 37 normal subjects The diabetic subjects had a shorter left ventricular ejection time, longer pre ejection period and a higher ratio of pre ejection period/left ventricular ejection time (P < 0 001) The isovolumic time was prolonged (P < 0 001) while heart rate and arterial pressure were within normal limits Abnormal function was independent of apparent duration and treatment by diet alone insulin or hypoglycemic agents On the basis of available morphologic data in human and canine diabetes an alteration of the myocardial interstitium may be the basis for this preclinical abnormality in diabetic patients

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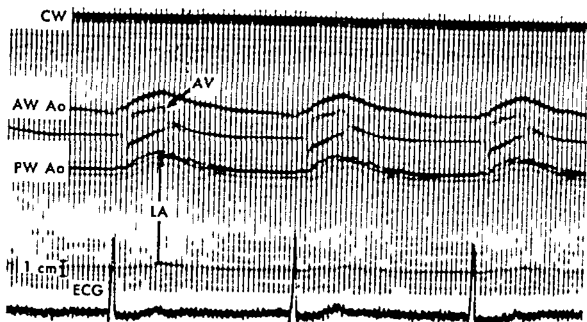


Fig 1 The left atrial dimension (LA) in a patient with mitral stenosis and enlarged left atrium CW = chest wall AW Ao = anterior wall of aorta PW Ao = posterior wall of aorta and AV = aortic valve

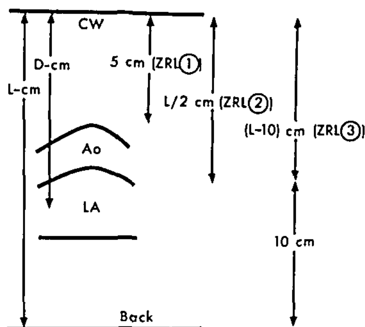


Fig 2 The diagram illustrates the chest wall (CW) the aortic root (Ao) and the left atrium (LA) L = anteroposterior diameter of the chest D = chest wall to mid left atrium distance and ZRL = zero reference level

tion to the sternal angle is that distance measured in the third or fourth interspace −x cm These values are given in Table I

Results

The individual results are shown in Table I and a summary of the data is given in Table II The mean AP diameter of the chest was 20 6 cm with a range of 15 to 25 5 cm Left atrial dimension varied from 2 cm to 6 8 cm The mean distance from anterior chest wall to mid left atrium (D) was 9 8 cm and the values ranged from 5 4 to 13 cm ZRL (2) had a mean value of 10 7 cm and the measurements varied from 5 to 15 5 cm The mean distance for mid chest (ZRL (3)) was 10 3 cm with a range of 7 5 to 12 8 cm The difference between the mean of D and ZRL (1) ZRL (2) and ZRL (3) is +4 8 cm −0 9 cm and −0 5 cm respectively No significant difference is present between D and ZRL (2) (r = 0 75 P = NS) and ZRL (3) (r = 0 75 P = NS) respectively However there is a significant difference (P < 0 01) between D and ZRL (1)

In Fig 3 the difference between D and the corresponding value for each of the three zero reference systems for a given patient (Y axis) is plotted against D (X axis) It is clear that D is consistently *greater than* ZRL (1) The difference between D and ZRL (1) varies from 0 4 cm to 8 cm (Fig 3) In 17 patients the difference was greater than 5 4 cm When D is compared with ZRL (2) there are differences ranging from zero to 4 8 cm and for ZRL (3) the values range from zero to 3 3 cm When ZRL (1) is compared with ZRL (2) there is a mean difference of 5 7 cm with a range of zero to 10 5 cm In five patients the difference was 9 5 cm of water or more

Discussion

Since the introduction of echocardiography by Elder and Hertz [4] this technique has been widely used to study normal and abnormal cardiac structures [5-8] The left atrial diameter can be

Table I

Name	*Ag*	*Sex*	*L* (cm.)	*D* (cm.)	*LA* (cm.)	*ZRL(2)* = (L 10) (cm.)	*ZRL(3)* = L/2 (cm.)
HR	63	M	25 5	13	3 5	15 5	12 8
RR	60	F	24 5	12 4	6 8	14 6	12 3
DG	44	M	24 5	11	3 6	14 5	12 3
VB	31	F	24 5	10 2	3 3	14 5	12 3
TM	30	M	23	8 2	3 2	13	11 5
GV	32	M	22	9 3	3 2	12	11
FP	45	M	23 5	11 5	6 0	13 5	11 8
FK	76	F	20 5	9 4	3 2	10 5	10 3
MR	64	M	24	11 5	3 8	14	12
FP	49	M	23	10 7	2 8	13	11 5
MY	31	M	22	9 5	3 4	12	11
HF	68	M	23	9 7	6 0	13	11 5
AC	57	M	24	11 6	3 6	14	12
BM	40	F	19	9	5 7	9	9 5
DG	63	F	21	9 3	5 0	11	10 5
BL	67	*F*	19	9	4 7	9	9 5
CC	53	M	24	11	3 2	14	12
VM	66	*F*	20	*10*	3.2	*10*	10
AF	16	M	25	12 5	3.2	15	12 5
FL	55	F	21	11	5 5	11	10 5
NK	49	F	19	11 2	3 7	9	9 5
RL	48	M	23	9 5	3 9	13	11 5
RV	64	F	19 5	9	4 7	9 5	9 8
Cl	38	F	17	8	4.3	7	8 5
OP	46	M	22	10	3 6	12	11 0
JG	55	M	19	9 3	3 3	9	9 5
ED	47	M	23	11 2	3 0	13	11 5
EL	17	M	18	8	3 2	8	9
VS	21	F	15	7 8	3 6	5	7 5
OS	79	F	17	7 3	2 8	7	8 5
MG	50	F	22.5	9 3	3 7	12 5	11 3
JL	79	M	20	11 2	3 5	10	10
HC	67	M	23	12 2	3 6	13	11 5
SB	56	M	22	12 3	3 8	12	11 0
EL	41	F	19	10 3	5 7	9	9 5
SE	55	M	18	9	2 8	8	9 0
PC	31	*M*	*19*	*10 10*	3 4	*9*	9 5
AL	31	M	19	9	2 0	9	9 5
AL	47	F	20	8 8	[illegible]0	10	10
PM	42	M	22	9 5	4 0	12	11
UB	30	M	21	9 5	3 0	11	10 5
KL	55	F	16	3	2 6	6	8
MR	19	M	19	8 4	3 0	9	9 5
MM	55	F	16	[illegible]5	5 0	6	8 0
HH	62	M	19 5	11 5	4 2	9 5	9 8
GL	25	F	15	5 4	2 0	5 0	7 5
AF	33	M	*19 5*	9 5	4 0	9 5	9 8
MS	55	M	21	10 5	5 0	11	10 5
EL	47	F	17	8	2 8	7	8 5
KN	35	F	19	8 8	3 2	9	9 5

L A te poste o diam ter f th chest in ntim ters
D Ch t w ll to m d l ft atrium distan e n ce t m te s
LA = Left t ial d m ns n in centim ters
ZRL = Zero ref ren l vel

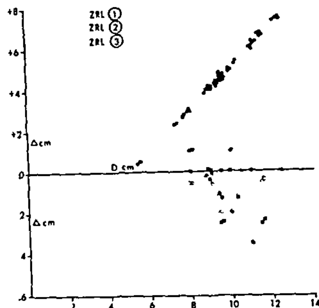


Fig 3 The difference (Δ) between D and ZRL (1) ZRL (2) ZRL (3) i e (D 5) cm D – (L–10) cm and (D – L/2) cm respec tively is plotted on the vertical axis, against D (horizontal axis) D = chest wall to mid left atrium distance

easily measured using ultrasound and has been found to correlate well with the angiographic left atrial area [9] Moreover these measurements of left atrial dimension have been shown to be reproducible from day to day [10] Thus the chest wall to mid left atrium distance can be quickly and accurately determined by echocardiography and this dimension can be used to compare three standard zero reference systems – ZRL (1) = 5 cm from the sternal angle ZRL (2) = 10 cm from the back and ZRL (3) = mid chest

There is no significant difference between ZRL (2) or ZRL (3) and D Hence they are valid ref erence systems Fig 3 shows that the scatter when ZRL (3) is used is less than with ZRL (2) Also ZRL (3) corresponds closely with D ir respective of the size of the chest or of the left atrium On the other hand a significant differ ence exists between ZRL (1) and D Since ZRL (1) is always less than D this reference system will consistently underestimate the left atrial pressure The maximum difference between ZRL (1) and D was 8 cm (Patient HR) Hence the er ror can be 8 cm of water or 6 mm Hg Similarly in 17 patients the error was greater than 5 4 cm of water or 4 mm Hg The diagnostic and therapeutic implications of underestimating the left atrial pressure are obvious For instance in

Table II

	L	D	ZRL (1)	ZRL (2)	ZRL (3)
Mean (cm)	20 6	9 8±0 22	5	10 7±0 4	10 3±0 2
Range (cm)	15 25 5	5 4 13	—	5 15 5	7 5 12 8

L = Anteroposterior diameter of the chest.
D = Chest wall to mid left atrium distance
ZRL = Zero reference level
The standard error is included with the means.

the case of Patient HR, cited above if the pressure measured by ZRL (1) is 10 mm Hg one would interpret this as being normal whereas the actual pressure is elevated at 16 mm Hg If the estimation based on ZRL (1) is 14 mm Hg then the correct pressure is 20 mm Hg and the therapeutic approach to the patient may have been different The data show that the error that results when ZRL (1) is used is greater in patients with large chests We must stress that these discrepancies apply mainly to left atrial pressure measurements and we have not attempted to assess the validity of these zero reference systems for the estimation of right atrial pressures

When the values for the three reference systems are compared the maximum difference is observed between ZRL (1) and ZRL (2) The mean difference if 5 6 cm the pressure difference would therefore be 5 7 cm of water or 4 2 mm Hg In five patients the difference was 9 5 cm or more i e , 7 mm Hg or more In these five patients a pressure of 13 mm Hg measured by ZRL (1) would read 20 mm Hg or more if ZRL (2) was used The difficulty that arises when comparing pressure data from laboratories that use different zero reference levels is readily apparent.

In summary the chest wall to mid left atrium distance was measured by echocardiography This dimension was compared with three standard zero reference systems The discrepancies that were observed are discussed Mid chest and 10 cm from the back are valid reference systems whereas 5 cm from the sternal angle consistently underestimates the left atrial pressure

Summary

This study compares the anterior chest wall to mid left atrial distance (D) determined by echocardiography with three standard cardiac zero reference levels (ZRL) (1) 5 cm from the sternal angle (2) 10 cm from the back (3) mid chest Echocardiography was performed on 50 subjects (16 normal subjects and 34 subjects with heart disease) Chest wall aortic root and left atrial echoes were obtained to measure D The AP diameter of the chest (L) was measured using calipers Thus ZRL (2) = (L−10) cm from the front of the chest and ZRL (3) = L/2 respectively

The difference between the mean of D and ZRL 1, ZRL 2 and ZRL 3 is +4 8 c.m −0 9 cm and −0 5 cm respectively Conclusions (a) ZRL (1) is consistently in error in 17 patients the difference was greater than 5 4 cm (b) there is no significant difference between D and ZRL (2) or ZRL (3), and hence they are valid reference systems, and (c) echocardiography can be used to accurately determine the zero reference level for left atrial pressure measurements

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The supra-additive natriuretic effect addition of bendroflumethiazide and bumetanide in congestive heart failure

Permutation trial tests in patients in long term treatment with bumetanide

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While thiazide diuretics and closely related drugs are moderately potent natriuretics and have proved very useful in the treatment of the early phases of congestive heart failure the highly potent natriuretics like furosemide ethacrynic acid or the new drug bumetanide are often required in the management of advanced heart failure[1,2] It is generally accepted that these two groups of diuretics differ in terms of renal tubular action The thiazides exert their major action in the distal renal tubules while the highly potent diuretics depress sodium reabsorption more extensively throughout the nephron including sites in the ascending limb of Henle s loop[1,6,7]

In a previous study it was demonstrated that in patients receiving long term treatment with large doses of furosemide and spironolactone the administration of a small dose of quinethazone or bendroflumethiazide was able to induce a supra additive natriuresis while an increase of furosemide dosage had no effect[8] This type of response is not only potentially useful in clinical work but is also of great pharmacodynamic interest

As a tentative explanation of this striking interaction between the two types of diuretics the following hypothesis was advanced during long term treatment with a highly potent diuretic like furosemide the depression of renal tubular sodium reabsorption at some sites in the nephron induces an accelerated sodium reabsorption at more distal sites because of an increased supply of sodium and because of activation of homeostatic mechanisms for sodium conservation[9,10] In this setting the administration of a small dose of a thiazide diuretic will be able to promote a supra additive natriuresis through its effect at the sites of accelerated sodium reabsorption[8]

Obviously further studies are necessary to support this hypothesis First the hypothesis implies that a similar response should be expected if other combinations of thiazides and highly potent diuretics are used Second the role of spironolactone for the response observed should be evaluated. The present study is designed to fulfill these demands through an examination of the natriuretic response to a single dose of bendroflumethiazide in patients with heart failure receiving long term treatment with the new highly potent natriuretic bumetanide This drug is very similar to furosemide in terms of renal tubular action and is equipotent with this diuretic in a weight ratio of 1 40[7] Furthermore the role of spironolactone for the natriuretic response is evaluated by means of variations of treatment programs

Material and methods

The patients consisted of 18 adult subjects with organic heart disease and signs of congestive heart failure requiring more intensive diuretic treatment The series included nine males and nine females Fourteen subjects had valvular heart disease two subjects had ischemic heart disease and two subjects had cardiomyopathy All patients had received digoxin and bume

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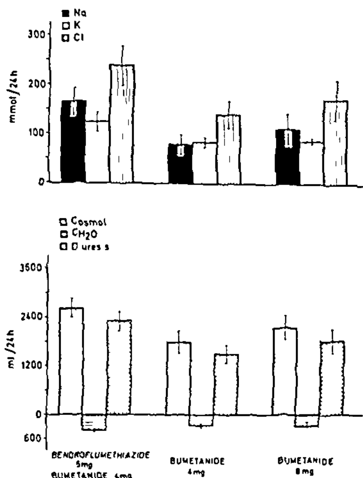


Fig 1 Mean values for urinary electrolyte and water excretion in relation to diuretic treatments in trial I Vertical bars indicate ± 1 standard deviation

Table I Sequence of administration of diuretic treatments

No of patients	Days of treatment		
	First	Second	Third
1	A	B	C
1	A	C	B
1	B	A	C
1	B	C	A
1	C	A	B
1	C	B	A

For explanation of A B and C see text.

tanide 4 mg (2 mg twice a day) for at least two weeks and no patients were off bumetanide before the trials All patients had received oral supplements of potassium chloride (45 mmol per day) and six patients had been given spironolactone, 25 mg four times a day for a similar period

During the study the patients received digoxin as before a 3 Gm sodium chloride *diet and fluid* intake of 1500 ml per day Bumetanide in a dosage of 4 mg daily was given as 2 mg at 9 A.M and 2 mg at 1 P.M and 8 mg daily was given as 4 mg at 9 A.M and 4 mg at 1 P.M Bendroflumethiazide was given as a single dose of 5 mg at 9 A.M. Twenty four hour urines were collected at 7 A.M. and blood samples were taken and body weight measured in the fasting state Serum and urine electrolytes and creatinine were determined, and osmolal and free water clearances were calculated as described previously[8]

Since the response to diuretic treatment varies not only with the drugs used, but also with the pathophysiologic status of the patient and with the sequence of administration of drugs the design of the study aimed at minimizing the effects of the latter variables The study was performed as permutation trial tests in which the drug treatment followed the rotation scheme shown in Table I This type of program ensures that within each trial all treatments are given to each patient and that each treatment has an equal chance of being used on the first second, or third day of the trial[11,13] A random allocation of patients to treatment programs was secured

In trial I, which included six patients receiving digoxin bumetanide 4 mg (= 2 mg, two times a day) and supplementary potassium chloride (45 *mmol per day) a comparison was made of the* effects of supplementary bendroflumethiazide 5 mg (A), of placebo (B) and of additional bumetanide 4 mg (= 2 mg, two times a day) (C)

In trial II which consisted of six patients receiving digoxin, bumetanide 4 mg (= 2 mg two times a day) spironolactone 100 mg (= 25 mg, four times a day) and supplementary potassium chloride (45 mmol per day) the effects of supplementary bendroflumethiazide 5 mg (A) of placebo (B) and of additional bumetanide 4 mg (= 2 mg two times a day) (C) were compared

In trial III which consisted of six patients receiving digoxin and supplementary potassium chloride (45 mmol per day) a comparison was made of the effects of bendroflumethiazide 5 mg (A) of bumetanide 4 mg (= 2 mg two times a day) (B) and of the combination bendroflumethiazide 5 mg plus bumetanide 4 mg (= 2 mg two times a day) (C)

Statistical analysis was performed by means of the Wilcoxson test for pair differences

Terminology *Dose addition describes the com*bined effects of two drugs acting on the same

Table II Statistical analysis of renal electrolyte water and solute excretion and of weight loss in trial I

Urinary excretion	Units	*Mean 24 h values ± S.E.M.* Bendroflume thiazide 5 mg + bumetanide 4 mg (A)	Bumetanide 4 mg (B)	Bumetanide 8 mg (C)	*Statistical significance of differences* A B	A C
Sodium	mmol./24 hours	167± 28	81± 21	113± 29	x	ns
Potassium	mmol /24 hours	125± 20	85± 10	88± 9	ns	ns
Chloride	mmol./24 hours	240± 42	142± 27	172± 39	x	ns
Diuresis	ml /24 hours	2 233±238	1,508±234	1 850±301	x	ns
Osmolal clearance	ml /24 hours	2 610±259	1 780±279	2 171±303	x	ns
Free water clearance	mL/24 hours	−377± 38	−272± 57	−321± 94	ns	ns
Creatinine	mmol./24 hours	9 08±1 40	9 05±1.37	9 40±1 81	ns	ns
Weight loss	Kg /24 hours	−1 03±0 50	−0 23±0 22	−0.36±0.27	ns	ns
Creatinine clearance	mL/min	50±6 1	50±7 5	52±4 7	ns	ns

n = p > 0 05 x = p < 0 05

receptors if doses of one drug are able to substitute for those of the other in proportion to their relative potency Deviations from dose addition are termed supra additive or infra additive and usually imply that the drugs act by different mechanisms

Effect addition or summation describes the combined effects of two drugs acting through different mechanisms when the response is equal to the sum of their individual effects Deviations from effect addition are usually termed supra additive or infra additive [8,14]

Results

Trial I This trial compared the effects of bendroflumethiazide 5 mg plus bumetanide 4 mg (A) of placebo plus bumetanide 4 mg (B) and of bumetanide 8 mg (C) in six patients (Fig 1) The results are shown with statistical analysis in Table II

A Bendroflumethiazide 5 mg plus bumetanide 4 mg compared to placebo plus bumetanide 4 mg (comparison A B) The mean value for renal sodium output was significantly higher after supplementary bendroflumethiazide (A) than after placebo (B) ($p < 0.05$) Similarly the urinary excretion of chloride water and osmolal clearance was significantly higher after A than after B ($p < 0.05$) A similar trend was found for renal output of potassium and for body weight loss.

B Bendroflumethiazide 5 mg plus bumetanide 4 mg compared to bumetanide 8 mg (comparison A C) The mean values for renal output of sodium chloride potassium water and osmolal clearance tended to be higher after supplementary bendroflumethiazide (A) than after additional bumetanide (C) but statistically significant differences were not obtained

C Serum electrolyte changes As shown in Table III the supplementary administration of bendroflumethiazide induces a significant decrease of serum potassium ($p < 0.05$) and an insignificant lowering of serum chloride, and a rise in standard bicarbonate Serum sodium is lowered while serum creatinine is unaffected.

Trial II This trial compared the effects of bendroflumethiazide 5 mg plus bumetanide 4 mg plus spironolactone 100 mg (A) of placebo plus bumetanide 4 mg plus spironolactone 100 mg (B) and of bumetanide 8 mg plus spironolactone 100 mg (C) in six patients (Fig 2) The results are given in Table IV

A. Bendroflumethiazide 5 mg plus bumetanide 4 mg plus spironolactone 100 mg compared to placebo plus bumetanide 4 mg plus spironolactone 100 mg (comparison A B) Renal output of sodium was significantly higher after supplementary administration of bendroflumethiazide (A) than after placebo (B) ($p < 0.05$) Similarly water and osmolal clearance was significantly higher after A than after B ($p < 0.05$) A similar trend was found for potassium and chloride excretion and for body weight decrease

B Bendroflumethiazide 5 mg plus bumetanide 4 mg plus spironolactone 100 mg compared to bumetanide 8 mg plus spironolactone 100 mg

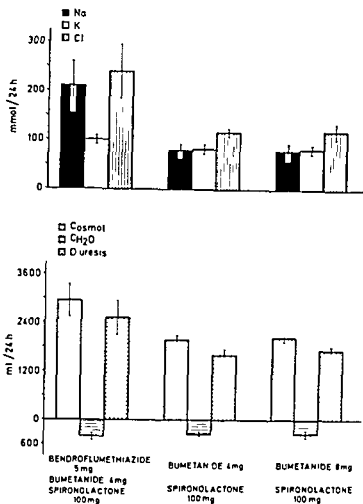


Fig 2 Mean values for urinary electrolyte and water excretion in relation to diuretic treatments in trial II Vertical bars indicate ± 1 standard deviation

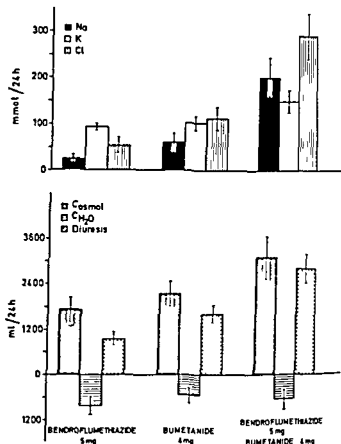


Fig 3 Mean values for urinary electrolyte and water excretion in relation to diuretic treatments in trial III Vertical bars indicate ± 1 standard deviation

(comparison A C) Similar to the findings above the renal output of sodium was significantly higher after bendroflumethiazide (A) than after additional bumetanide (C) ($p < 0.05$)

Trial III This trial compares the effects of bendroflumethiazide 5 mg (A) of bumetanide, 4 mg (B) and of bendroflumethiazide 5 mg plus bumetanide 4 mg (C) The results are shown in Tables V through VI and in Fig 3

A Results of statistical analysis Although the responses to bumetanide 4 mg (B) were slightly higher than those after bendroflumethiazide, 5 mg (A) no significant differences were present except for the diuresis However the effects of the combination of drugs (C) in terms of renal outputs of sodium potassium, chloride water and osmolal clearance were significantly higher than those of other treatments as shown by the comparisons (A C) and (B C) ($p < 0.05$) (Table V and Fig 3) Creatinine clearance and free water clearance were unaffected

B Net effects of the combination of drugs The differences (C − (A + B)) i e the response to the combination of drugs minus the sum of the responses to individual drugs calculated for each patient are assumed to represent the net effects of the combination of diuretics Actually this estimate presumes that urinary excretion is equal to zero without treatment and it seems likely, therefore that the net effects are underrated. Nevertheless in terms of urinary sodium and chloride outputs the differences (C − (A + B)) are positive and statistically significantly different from zero ($p < 0.05$) (Table VI)

These results clearly indicate that the effects of the combination of bendroflumethiazide and bumetanide in this setting represent a supra additive natriuretic effect addition

Discussion

The present study demonstrates that bendroflumethiazide in a small dosage is able to induce a significant natriuretic and diuretic effect when given as supplementary treatment to patients with heart failure in long term treatment with bumetanide This is in accordance with our

Table III Statistical analysis of serum electrolyte changes in trial I

Serum values	Units	Mean 24 hour changes ± S.E.M. for each treatment: Bendroflume thiazide 5 mg + bumetanide 4 mg (A)	Bumetanide 4 mg (B)	Bumetanide 8 mg (C)	Statistical significance of differences: A B	A-C
Sodium	mmol./L.	−1 83 ± 0 30	0 66 ± 1.33	1 50 ± 0 76	ns	x
Potassium	mmol./L	−0 45 ± 0 14	0 21 ± 0 14	−0 01 ± 0 00	x	ns
Chloride	mmol./L.	−2 50 ± 1.51	−0 33 ± 1 38	−1 16 ± 1 24	ns	ns
Standard bicarbonate	mmol./L	1 20 ± 0 78	0 48 ± 0 50	0.28 ± 0 71	ns	ns
Creatinin	mmol./L.	0 01 ± 0 00	0 00 ± 0 00	0 00 ± 0 00	ns	ns

ns p > 0 05 x p < 0 05

Table IV Statistical analysis of renal electrolyte water, and solute excretion and of weight loss in trial II

Urinary excretion	Units	Mean 24 hour values ± S.E.M.: Bendroflume thiazide 5 mg + bumetanide 4 mg + spironolactone, 100 mg (A)	Bumetanide 4 mg + spironolactone 100 mg (B)	Bumetanide 8 mg. + spironolactone 100 mg (C)	Statistical significance of differences: A B	A C
Sodium	mmol /24 hours	209 ± 50	81 ± 13	79 ± 16	x	x
Potassium	mmol./24 hours	101 ± 8	84 ± 11	84 ± 8	ns	ns
Chloride	mmol./24 hours	204 ± 54	117 ± 8	121 ± 17	ns	ns
Diuresis	ml./24 hours	2 533 ± 437	1 626 ± 131	1 688 ± 98	x	ns
Osmolal clearance	ml /24 hours	2 951 ± 409	1 983 ± 110	2 053 ± 109	x	ns
Free water clearance	ml /24 hours	−418 ± 88	−353 ± 67	−365 ± 77	ns	ns
Creatinine	mmol /24 hours	7 86 ± 1 04	7 72 ± 0 40	7 22 ± 0 58	ns	ns
Weight loss	Kg /24 hours	−1 13 ± 0 44	−0 22 ± 0 18	−0 35 ± 0 14	ns	ns
Creatinine clearance	ml./min.	52 ± 9 88	49 ± 6 98	46 ± 8 22	ns	ns

ns p > 0 05 x p < 0 05

previous study of the effect of supplementary administration of quinethazone or bendroflumethiazide to patients receiving long term treatment with furosemide[8] In both studies the design of the experiments permitted an evaluation of drug effects separately from the influence of different patients and in varying sequence of administration of drugs

In the present study the long term diuretic was the new highly potent drug bumetanide which on a weight basis is the most powerful diuretic available today[2 7] In terms of renal tubular action bumetanide shows many similarities with furosemide and has been found to be equipotent with the latter drug in a weight ratio of 1 40[7] Apparently both drugs are acting on the same receptors in the nephron including sites in the ascending limb of Henle s loop and probably also in the proximal and distal segments[1 7] In patients receiving long term treatment with these highly potent drugs a significant increment of urinary sodium and water excretion has been induced by administration of a small dose of bendroflumethiazide or of the closely related drug quinethazone These latter diuretics are very similar in terms of natriuretic potency and have a major site of action in the distal renal tubules[1]

In our previous study all patients received spironolactone which has an entirely different

Table V Statistical analysis of renal electrolyte, water, and solute excretion and of weight loss in trial III

Urinary excretion	Units	Mean 24 hour values ± S.E.M. Bendroflumethiazide 5 mg (A)	Bumetanide 4 mg (B)	Bendroflumethiazide 5 mg + bumetanide 4 mg (C)	Statistical significance of differences A B	B C	A C
Sodium	mmol/24 hours	25 ± 9	65 ± 20	206 ± 47	ns	x	x
Potassium	mmol/24 hours	94 ± 9	104 ± 14	152 ± 24	ns	x	x
Chloride	mmol/24hours	56 ± 20	114 ± 25	296 ± 51	ns	x	x
Diuresis	ml/24 hours	973 ± 168	1 631 ± 251	2 821 ± 405	ns	x	x
Osmolal clearance	ml/24 hours	1 775 ± 319	2 148 ± 323	3 466 ± 593	x	x	x
Free water clearance	ml/24hours	−802 ± 255	−517 ± 201	−645 ± 238	ns	ns	ns
Creatinine	mmol/24 hours	11 52 ± 1 05	12 3 ± 2 79	13 4 ± 3 04	ns	ns	ns
Weight loss	Kg/24 hours	−0 05 ± 0 31	−0 13 ± 0 33	−1 55 ± 0 51	ns	ns	ns
Creatinine clearance	ml/min	72 ± 13	71 ± 16	84 ± 21	ns	ns	ns

ns $p > 0.05$ x $p < 0.05$

Table VI Net effects of combination of drugs in trial III (C − [A + B]) For explanation of A B and C, see Table V and text

Parameters	Units	Mean ± S.E.M. (C)	(A + B)	Statistical significance of differences (C − [A + B])
Urinary sodium	mmol/24 hours	206 ± 47	90 ± 16	$p < 0.05$
Urinary chloride	mmol/24 hours	296 ± 51	170 ± 22	$p < 0.05$

type of action in the renal tubules [8] However, it is apparent from the present study that spironolactone is of no significance for the effect addition observed since the trials I and III were performed without the administration of spironolactone

The results obtained in trial III convincingly demonstrate that in terms of natriuresis and chloruresis, the combined effects of bendroflumethiazide and bumetanide represent a supra additive effect similar to the results obtained with the combination of quinethazone and furosemide [8] In both studies the creatinine clearances were unaffected during diuresis suggesting that the response is not related to changes in glomerular filtration rates but rather due to alterations in tubular sodium reabsorption

A tentative explanation of the supra additive effect addition observed is given schematically in Fig 4 The renal tubular reabsorption of sodium represents a sum of multiple discrete functions throughout the nephron A major part of sodium is reabsorbed in conjunction with chloride or bicarbonate as represented by the arrows to the left and in the middle of the upper panel of the diagram A minor fraction is reabsorbed in exchange with potassium in the distal tubules as shown by the arrow to the right

During the long term administration of a highly potent diuretic the drug will depress the reabsorption of sodium in conjunction with chloride at several sites in the nephron and through this effect accelerate sodium reabsorption at more distal sites by means of the increased supply of sodium and by means of homeostatic mechanisms activated during natriuresis [9,10] This type of action will also accelerate the sodium potassium exchange in the distal tubules This pattern of action is shown in the middle panel of Fig 4

In this setting it becomes possible for a second less potent diuretic, through its action at the sites of accelerated reabsorption to promote a more marked natriuresis than it would be able to in

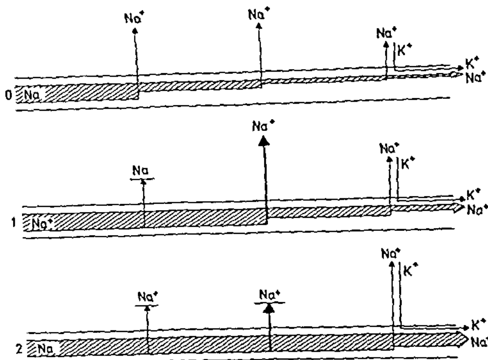


Fig 4 Theoretical schematic diagram of the combined effects of diuretics upon renal tubular *sodium transport*. A detailed explanation is given in the text.

duce when used alone Because of the increased delivery of sodium to the exchange sites and due to activation of homeostatic mechanisms for sodium conservation the potassium excretion in conjunction with chloride is further increased This interaction of drugs is shown in the lower panel of Fig 4

It appears from Tables II and III that supplementary administration of bendroflumethiazide in this particular setting results in an increased output of potassium and promotes the development of hypokalemia with a trend for hypochloremia and metabolic alkalosis As shown in Table IV the concomitant use of spironolactone appears to be able to decrease the potassium loss although it is not eliminated

A clinical corollary to these findings is that supplementary use of a thiazide diuretic in patients receiving long term treatment with highly potent natriuretics involves a risk of development of potassium loss hypokalemia hypochloremia and metabolic alkalosis and an associated risk of precipitation of digitalis toxicity It seems advisable therefore that extra supplements of potassium chloride or of potassium saving diuretics should be considered in this setting in order to prevent severe disturbances in electrolyte metabolism

Summary

The additive natriuretic effect of a single dose of bendroflumethiazide 5 mg has been studied in patients with advanced congestive heart failure in long term treatment with bumetanide 4 mg daily Three permutation trial tests were performed including six patients each In the first trial the response to supplementary bendroflumethiazide 5 mg was definitely superior to that of additional bumetanide 4 mg in terms of renal output of sodium chloride potassium water and osmolal clearance In the second trial a similar pattern was found in patients receiving a combination of bumetanide 4 mg and spironolactone 100 mg daily The third trial compared the effects of bendroflumethiazide 5 mg plus bumetanide 4 mg of bendroflumethiazide 5 mg and of bumetanide 4 mg In terms of natriuresis and chloruresis the response to the combination of two drugs was significantly larger than the sum of the effects of other treatments

It is concluded that the combined effects of the drugs represent a supra additive effect addition

for sodium and chloride A tentative explanation of the mechanism of interaction in terms of inhibition of renal tubular sodium transport is given

Since the combined effects of the two drugs independent of supplementary spironolactone, involve a tendency to development of hypokalemia, hypochloremia, and alkalosis, it is recommended that supplementary use of bendroflumethiazide in this setting is combined with the administration of potassium chloride or potassium saving diuretics

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Diagnostic importance of aortography in conal ventricular-septal defect

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Aortic insufficiency (AI) frequently develops from the aortic valve s prolapse into the ventric ular septal defect (VSD) This occurs even when the defect is rather small and left to right shunt is not severe The differential incidence rate of conal VSD associated with a prolapsing aortic valve and subsequent AI (prolapsing AI) among Western countries[1,2] and Japan[3] is worthy of notice being roughly 60 per cent for the latter

In cases of VSD having already developed aortic regurgitation complete elimination of AI by simple closure is rarely achieved[4,5] In those cases of VSD associated with a more than three year continuation of AI surgical procedures of aortic valvuloplasty or valve replacement are necessary to provide relief[6] It appears reasonable to assume that if thoracic aortography is routinely employed and surgical closure of the VSD is effected in all cases of conal VSD with prolapsed aortic valve prior to onset of AI the over all occurrence of VSD with AI can be reduced by approximately one half

In order to assess this assumption retrograde thoracic aortography was performed on twenty four patients with conal VSD This report presents the aortographic findings thus obtained, and provides cogent evidence of the benefits of aortography in cases of asymptomatic conal VSD

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Materials and methods

Twenty four patients, including two Chinese diagnosed to have a conal VSD in the outpatient department were admitted to this institute from July 1971 to August 1973 A resume of their pertinent features is given in Table I In all cases routine physical examinations electrocardiography chest roentgenography right heart catheterization and retrograde thoracic aortography were undertaken Aortography was performed by injection of the contrast medium through a NIH catheter (No 6 to No 9) inserted via the right femoral artery to the portion immediately above the aortic valve Conray 400 of 1 5 ml per kilogram or angioconray of 0 8 ml per kilogram was injected within 1 5 seconds by a pressure injector (Gidrund, Elema Schoenander) In the early series a biplane film exchanger (AOT Elema Schoenander) was employed most often to obtain the serial aortograms The unit of choice gradually shifted to a monoplane 35 mm roentgenocinematography (GV 35 Eclair) and in the last ten cases cinematography was used exclusively Cine film speed was set at 100 frames per second and the patients were placed in a right anterior oblique position of 40 to 60 degrees as this speed and position were deemed most appropriate for capturing fine movements and for tangential visualization of the prolapsed section of the aortic valve Surgical correction of the VSD was performed in twelve cases In nine of these cases the aortic valve s prolapse was ascertained aortographically and in the remaining three cases the valve s prolapse was not revealed but the left to right shunt ratio exceeded 30 per cent

Table I Summary of clinical findings of 24 patients with the conal VSD

Case No	Sex	Age (y)	PMI of HM(IS)	ECG	Chest x ray CTR (%)	Chest x ray PBF	RHC (%) L to R shunt	Aortography AOT	Aortography Cine	Aortography Aortic valve	Operation	Remarks
1	M	25	2nd	N	45	N	29			Prolapse	Done	
2	M	6	2nd	N	49	N	Uncalculable			Nonprolapse		
3	M	10	2nd	N	46	N	9			Prolapse	Done	
4	M	6	3rd	N	50	N	7			Nonprolapse		
5	F	6	3rd	LVH	55	INC	33			Prolapse	Done	
6	M	7	2nd	N	50	N	19			Nonprolapse		
7	F	7	3rd	LVH	45	INC	22			Prolapse	Done	
8	M	10	3rd	BVH	52	INC	26			Prolapse	Done	
9	M	7	2nd	N	48	N	Uncalculable	*		Nonprolapse		Two chambered RV
10	F	14	2nd	N	43	N	11	*	*	Nonprolapse		
11	F	7	3rd	N	48	N	29		*	Prolapse	Done	Chinese mild AI
12	M	4	2nd	N	55	N	10	*		Nonprolapse		
13	F	9	2nd	LVH	50	INC	37			Nonprolapse	Done	Bicuspid AV
14	M	6	1st	N	45	N	8	*		Nonprolapse		
15	M	4	3rd	BVH	50	INC	31		*	Nonprolapse	Done	
16	M	10	2nd	N	—	—	22			Nonprolapse		
17	F	27	2nd	N	47	N	27			Nonprolapse		Mild MI
18	F	11	2nd	LVH	60	INC	20			Prolapse		
19	M	11	3rd	LVH	51	INC	53		*	Nonprolapse	Done	
20	M	11	3rd	N	43	INC	29		*	Prolapse	Done	
21	M	14	3rd	BVH	48	INC	30			Nonprolapse		
22	F	16	2nd	N	47	INC	19			Nonprolapse		Two chambered RV
23	M	10	2nd	LVH	50	N	24			Prolapse	Done	Chinese
24	M	6	2nd	N	45	INC	36			Prolapse	Done	

M male F female PMI punctum maximum of intensity HM heart murmur IS intercostal space ECG electrocardiogram CTR cardio-thoracic ratio PBF pulmonary blood flow N normal LVH left ventricular hypertrophy BVH biventricular hypertrophy INC increasing RHC right heart catheterization L to R shunt left to right shunt ratio AOT biplane large film aortography cine cine aortography RV right ventricle MI mitral insufficiency and AV aortic valve

Results

On auscultation the first heart sound was within the normal range except for case No 19 in which it was diminished Pulmonary second sound was normal in all cases Harsh crescendo decrescendo pansystolic or long ejection systolic murmurs were audible in all cases Their point of maximum intensity was in the left first to third intercostal area The peak of the ejection systolic murmur was noted mainly in the late systolic phase In a few cases however the peak was in the early systolic phase The point of the murmur s maximum intensity was one or two intercostal spaces higher in conal VSD than in subcristal VSD In six cases a thrill was palpable at the point of the murmur s maximum intensity A faint diastolic inflow murmur was heard at the apex in four cases (Nos. 5 13 15 and 19) There were no distinctive differences noted between the cases with and without aortic valve prolapse

Electrocardiography revealed either mild left ventricular or combined ventricular hypertrophy in nine cases The remaining fifteen cases were asymptomatic in this respect The cardiothoracic ratio was more than 50 per cent in ten cases as indicated by chest roentgenograms Pulmonary vascularity was normal or only slightly increased in all instances except case No 19 which showed a moderate increase in the pulmonary blood flow

On right heart catheterization ventricular and pulmonary arterial pressures were normal except in cases Nos 9 and 22 where stenosis resulted from an anomalous muscle band in the right ventricle Systolic pressure in the ventricu



Fig 1 Three different phases of a serial aortogram of case No 7 in the right lateral projection *A*, diastole A large protrusion is seen at the right coronary sinus and double contour (marked with arrows) is formed between the protruded aortic valve and the natural contour of the sinus *B* early systole The protrusion of the sinus bulges hugely *C* midsystole The protruded portion (marked with white arrows) becomes most prominent in this series



Fig 2 Three different phases of an aortogram of case No 8 *A* diastole Double shadow is seen at the bottom of the right coronary sinus (indicated by arrows) *B* early systole The lowest part of the sinus bulges anteriorly in a moment (marked with an arrow) *C*, midsystole The bulge disappears and only proper contour of the right coronary sinus is revealed

lar inflow tract was elevated to 39 mm Hg (case No 9) and 51 mm Hg (case No 22) Mild systolic pressure gradients were also observed between the outflow and inflow tract in these two cases Left to right shunt ratio was about 30 per cent or less except in case No 19 where it was 53 per cent. In cases Nos 2 and 9 shunt was below the calculable level In these two cases protrusion of the aortic valve was not revealed by aortography Consequently lack of left to right shunt indicated only that these have a small VSD

On aortography prolapse of the aortic valve was observed with clarity in ten of the twenty four cases invariably located on the right coronary sinus of Valsalva In one case (No 7) it was huge observable throughout systole and diastole In the remaining nine cases it was rather small The aortic valve s prolapse was noted during both systolic and diastolic phases in cases Nos 4 7 20 and 27 In case No 8 it was noted during diastole and early systole In cases Nos 1 3 18 and 24 the prolapse was observed throughout systole or only in early systole but never in diastole

Fig 1 reveals three different phases of case No 7 s serial aortography in right lateral projection In diastole (Fig 1 *A*) anterior protrusion of the aortic valve beyond its natural contour is observable in the middle section of the right coronary sinus (see arrows) This prolapsed area enlarged further in systole reaching its maximum in mid systole (Fig 1 *C*) At operation a semilunar shaped VSD with a maximum diameter of 15

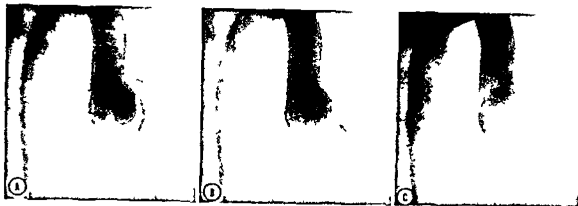


Fig 3 Three different phases of a cineaortogram of case No 11 in a right anterior oblique position of 60 degrees. *A* diastole Contour of the right coronary sinus is smooth *B* early systole A small protrusion appears in the middle lower level of the right coronary sinus (indicated by an arrow) *C* midsystole The protrusion is visualized faintly on the high speed cine aortography but clear presentation in a stationary film is impossible

mm was located just below the pulmonary valve s annulus A section of the right coronary cusp and sinus was prolapsed into the right ventricular cavity through the VSD The over all aspects of the right ventricular outflow tract were similar to those shown in Fig 4

The right lateral views of a serial aortography for case No 8 are displayed in Fig 2 In diastole (Fig 2 *A*) a small protrusion was distinctly revealed at the right coronary sinus base (see arrows) In early systole (Fig 2, *B*) the prolapsed aortic cusp was drawn into the VSD and protruded anteriorly (see arrow) In midsystole however it disappeared (Fig 2 *C*) At operation a small round VSD 10 mm in diameter was found in the proximal part of the conal septum There was a small muscle band between the superior margin of the VSD and the pulmonary valve annulus but none existed between the defect s inferior margin and the tricuspid valve annulus Therefore it appears reasonable to classify this as a subcristal VSD The lumen was nearly occluded by the prolapsed right coronary cusp

Fig 3 contains right anterior oblique views of a cineaortogram of case No 11 a Chinese girl In diastole (Fig 3 *A*) the right coronary sinus contour is smooth and the protrusion is not visible In early systole (Fig 3 *B*) a small protrusion appears over the right coronary sinus lower part (see arrow) It is faintly observable in midsystole as well (Fig 3 *C*) but again disappears in diastole The findings at operation were indentical to those shown in Fig 4 although the VSD was smaller

Surgical closure of VSD was performed in twelve cases A longitudinal incision was routinely made over the outflow portion of the right ventricular wall with the aid of complete extracorporeal circulation In nine cases of prolapsed aortic valve with the exception of case No 8 (subcristal VSD) semilunar shaped VSD s ranging from 7 to 15 mm in length were observed in the subpulmonary conal septum Fig 4 reveals case No 20's right ventricular outflow tract at operation A semilunar shaped VSD is located in the conal septum below the right pulmonary cusp annulus The defective lumen is almost obstructed by the prolapsed right coronary cusp The white fibrous tissue (see * mark) observable between the prolapsed aortic cusp and the right pulmonary cusp annulus (see dotted line) is actually the right coronary sinus exposed to the right ventricular side owing to a regional deficiency in the conal muscle This right coronary sinus as well as the prolapsed right coronary cusp bulged toward the right ventricular cavity when the cross clamp previously applied to the ascending aorta was released

In three cases without aortic valve prolapse on aortogram the VSD s location and size were identical to those with prolapsing aortic valve However aortic valve prolapse and regional deficiency in the conal muscle were not observed

In all operated cases VSD was closed directly with an over and over continuous suture or with a series of a few interrupted sutures and reinforced with several additional sutures The patient s postoperative courses were smooth and uneventful

Discussion

In Europe and America VSD with AI has been considered rather rare Its incidence rate appears to be about 4 to 7 per cent of all isolated

Table II Comparison of the anatomic position of VSD in autopsied hearts with isolated VSD reported in the United States and in Japan

Position of VSD	Becu[15] Goor[16]	Tatsuno[13] Shohtsu[14]
Subpulmonary VSD	13 (8%)	34 (29%)
Subcristal VSD	10ɔ (73%)	78 (68%)
Common AV canal type VSD	7 (4%)	1 (1%)
Muscular defect	32 (15%)	2 (2%)

This c teg ry of the VSD includes the subpulmonary VSD and the midcristal VSD

VSD [7,11] In contrast the rate is much higher in Japan somewhere around 10 per cent One plausible explanation for this difference is that in Japan conal VSD itself is considerably higher [3,12] Table II compares the various VSD s anatomic positions as indicated by Japanese literature[13,14] and Becu and co workers [15] and Goors and co workers [16] reports The Japanese conal VSD (sub pulmonary) incidence rate is 3 5 times higher than that of the American one Prolapsing AI ap pears to be frequently associated with conal VSD regardless of the cultural context.[3,17] Table III shows the cases of isolated VSD operated on dur ing the last eight years at this institute There were 174 cases of conal VSD (66 cases or 38 per cent were associated with prolapsing AI) and 364 cases of subpulmonary VSD (6 cases or 1 6 per cent were associated with prolapsing AI) Thus it appears that prolapsing AI is twenty times more prevalent in conal VSD than in subcristal VSD

Once the AI has developed in cases with VSD simple closure of the defect sometimes fails to relieve the AI [4] Ever since Garamella and co workers[18] reported the first successful surgical correction a variety of direct operative pro cedures including aortic valvuloplasty[8,10,19] or valve replacement [4,5,20] have been developed However recommendation of simple closure of the VSD in patients with minimal AI has been rarely reported.[21,23] Of our institute s 106 oper ated patients with VSD and AI simple closure was performed in sixty eight cases In twelve of these cases AI disappeared postoperatively and in thirty cases its severity was reduced. In the re mainder of the cases it either remained stable at the preoperative level or worsened Even though simple closure of the VSD was mainly employed in young patients in the syndrome s early devel



Fig 4 Operative view of the right ventricular outflow tract of case No 20 The conus septum and the pulmonary valve (PV) are revealed through the longitudinal incision made on the outflow tract of the right ventricle A small semilunar shaped VSD is located below the pulmonary valve annulus (marked with a dotted line) the lumen of the defect is obstructed almost entirely by the prolapsed aortic valve (AV) At the right upper area of the VSD immediately below the right pulmonary cusp white fibrous tissue (marked with *) is seen This is a part of the right coronary sinus of Valsalva

opmental stage AI remained somewhat intract able for the largest percentage Accordingly surgical intervention to the deformed aortic valve for correction of AI does not appear to be warranted in older patients and those with AI of a more severe nature In our experience [6] if more than three years have elapsed since the onset of AI aortic valvuloplasty is the method of choice Should more than six years have passed, aortic valve replacement is generally warranted. Ob viously these factors support the assertion that early discovery of either established or impend ing aortic valve prolapse in conal VSD cases and rapid intervention is important for successful long term patient management

Table III Comparison of anatomic position of VSD in surgical cases of isolated VSD, VSD with AI, and VSD with prolapsing AI

(From April 1966 to August 1973)

Position of VSD	*Isolated VSD*	*VSD with AI*	*VSD with prolapsing AI*
Subpulmonary VSD (conal VSD)	152	83	60
Midcristal VSD (conal VSD)	22	9	6
Subcristal VSD	364	14	6
Persistent common AV canal type VSD	10	–	–
VSD in trabeculated muscular septum	3	–	–
Total	551	106	72

Conal VSD is readily distinguishable from subcristal or other VSD s by auscultation Stein feld and co workers[24] stated that the site of the systolic murmur s maximum intensity in sub pulmonary VSD was the left second intercostal space The murmur itself was pansystolic and crescendo decrescendo in quality The charac teristic subcristal VSD murmur is located in the left second third or fourth intercostal spaces radiating in varying degrees over the precor dium It tends to be somewhat harsh pan or nearly pansystolic in duration and of a fairly uniform amplitude throughout While Farrú Duffau and Rodriguez [25] opinion was concurrent with the above description they added that the characteristic subpulmonary VSD murmur was holosystolic with conspicuous late systolic accen tuation Our auscultatory and phonocar diographic findings were virtually identical with those of these authors

Aortography is absolutely necessary for ascer taining the aortic cusp s prolapse with relation to the VSD There have been reports[26 27] that left ventriculography was performed to ascertain the VSD s position or to diagnose for multiple VSD However, in order to observe fine movements of the aortic valve, aortography is more advan tageous With cineaortography, the patients positions can be freely changed in order to best capture the aortic cusp s prolapsed portion in tangential axis High speed photographs are also attainable Thus cineaortography is the most highly recommended diagnostic technique

Conclusion

Retrograde thoracic aortography was per formed on twenty four patients diagnosed as having conal VSD In ten of the twenty four cases the aortic valve prolapse was identifiable while in the remaining fourteen cases it was not. Surgical closure of VSD was undertaken in nine cases with prolapse and in three cases without prolapse but whose left to right shunt ratio was in excess of 30 per cent Conal VSD is highly cor related with the appearance of prolapsing AI, and is readily distinguishable by auscultation from other VSD s Once AI has occurred deform ity of the prolapsed aortic valve progress rapidly, and complete relief becomes difficult without direct intervention on the aortic valve Accor dingly in the patients with a conal VSD prior to onset of AI aortography should be carried out, and in cases with aortic valve prolapse VSD closure should be effected With such routine measures a good half of the cases of VSD with AI can be prevented

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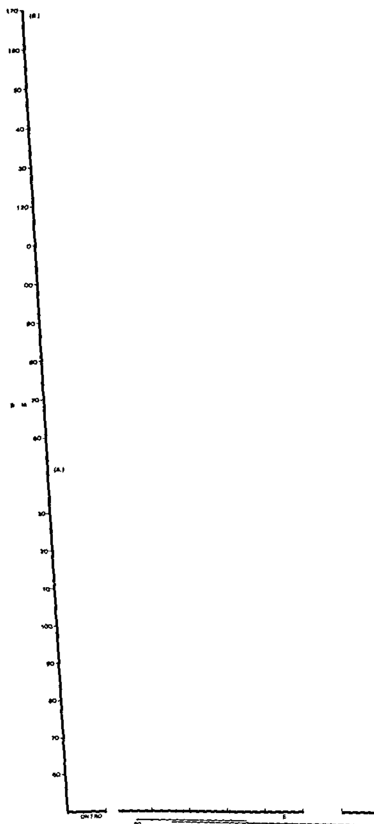


Fig 1 Beat to-beat plot of HR of five subjects at A, 50 watts B 150 watts For explanation of abscissa segments A to E and significance of underscoring see text, first paragraph under Results

Immediate cardiac response to exercise physiologic investigation by systolic time intervals at graded work loads

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Investigations of the cardiac response to both isometric and rhythmic exercise indicate striking increments in heart rate immediately following the onset of exertion[1-3] In most other studies involving cardiocirculatory responses changes have been measured at minute to minute intervals or over periods of several minutes so that many of the earliest responses have not been investigated Systolic time intervals recorded during ergometer exercise demonstrated that the major changes in many parameters had occurred by the first minute[4] Changes in systolic time intervals (STI) reliably reflect the physiologic effects of exercise[4-6] have now been successfully measured during actual exercise performance[4] and are especially suited to beat to beat analysis of rapid changes in cardiac function (e g the Valsalva maneuver)[7] To quantitate and identify the actual onset of the earliest responses to exercise we measured and statistically analyzed the STI at various exercise loads and plotted these graphically on a beat to beat basis

Methods

Subjects The subjects were five healthy normally active male volunteers aged 23 to 29 each had a normal physical examination history and 12 lead electrocardiogram (ECG)

Recordings A bipolar sternal ECG lead used for monitoring exercise was recorded as previously described.[4] An HP Model 21051 A/B contact sensor was used to record the phonocardiogram (PCG) in the meso apical area at a nominal filter frequency of 50 Hz. A Sanborn microphone No 374 and funnel pick up were used to record the right carotid pulse curve with filter cut offs at 0 15 and 20 Hz Recordings were made at a paper speed of 75 mm per second on a Hewlett Packard optical recorder No 568 1004

Protocol Subjects performed sitting exercise on a Collins bicycle ergometer at three separate work loads 50 100 and 150 watts The pedaling rate was standardized at 60 r p m A fifteen minute rest period preceded each of the three exercise sessions Resting heart rate was observed on the true heart rate meter of a Collins Cardiotachimetric Controller Subjects were considered to be in steady control state when the heart rate remained stable for several minutes

Pre ejection period was not corrected for heart rate because atrial pacing has shown that this interval does not change in the same individual with rate per se although both may change simultaneously under adrenergic effects General relationships between pre ejection period (PEP) and heart rate (HR) in pooled interindividual data are ascribed to differences in adrenergic influences

Measurements Heart rate (HR), pre ejection period (PEP) corrected ejection time (ET_c) the ratio of pre ejection period to left ventricular ejection time (PEP/LVET) and pulse transmission time (PTT) were measured as previously described[4]

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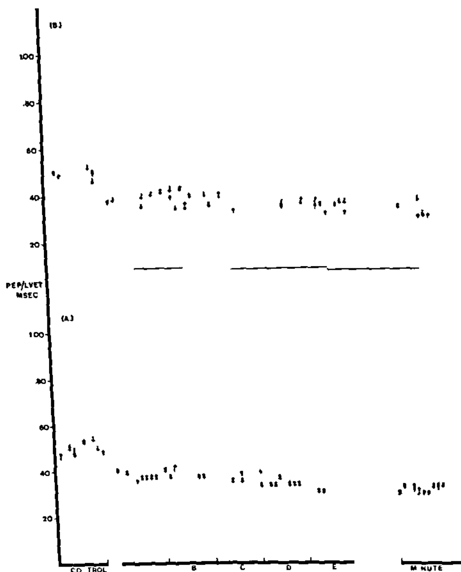


Fig 3 Beat to beat plot of pre ejection period and left ventricular ejection time ratio of five subjects at *A* 50 watts *B* 150 watts For explanation of abscissa segments A to E and significance of underscoring *see text*, first paragraph under Results

than 1 per cent the Duncan s New Multiple Range Test (DNMRT)[10] was used to determine the exact location of these differences

Results

Mean values and standard errors for all measurements are summarized in Table I Beat to beat plots are illustrated in Figs. 1 through 4 a b c d, and e in Table I correspond respec tively to 10 beat segments A B C D and E in Figs 1 through 4 Results during any periods un derscored by the same line did not differ signifi cantly Periods not underscored by the same line did differ significantly ($p < 0\ 01$)

Table I includes results for all exercise loads For concise representation the Figures show results at the low (50 watt) and high (150 watt) loads

Heart rate (HR Table I Fig 1) HR increased from control to one minute of exercise The most striking change in HR occurred within the first few beats of exercise and was of equal magnitude at all *loads* However *HR* was subsequently af fected by the level of exertion in that by the end

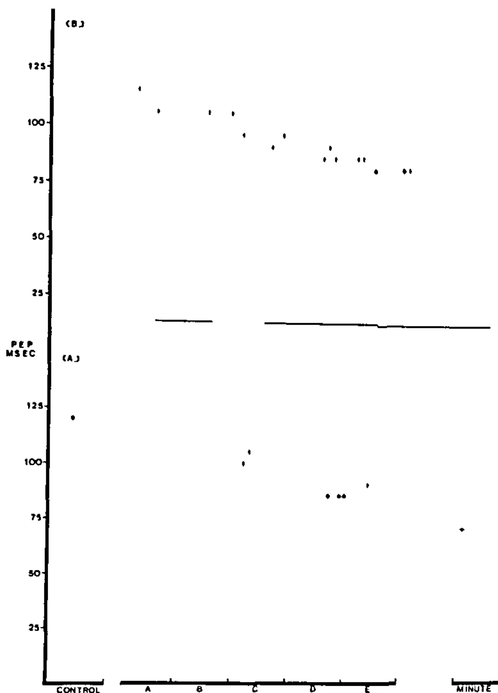


Fig 2 Beat to beat plot of pre ejection period of five subjects at *A* 50 watts *B* 150 watts. For explanation of abscissa segments A to E and significance of underscoring *see text*, first paragraph under Results

Statistical analysis Control values for each subject were represented as the mean value of 10 beats recorded at the end of the rest period Because of transient motion artifact when sub jects began pedaling the onset of the measure ment period began when the subject reached the pre set pedaling rate of 60 r p m In practice this involved discarding only the first four to six beats For statistical analysis the initial fifty beats measured during exercise were divided into sections of ten beats each with the mean value representing that period for each subject

Although this investigation concerns early exer cise responses the mean value of ten beats at one minute of exercise was also determined for each subject to insure directional comparability with reported studies of exercise responses which have been measured on a minute to minute basis A Randomized Blocks Design was the analysis of variance used to determine whether statistically significant differences existed among control se quential segments during the initial fifty beats of exercise and the one minute values When F values yielded per cent points equal to or less

d	e	*1 minute*
108 6 ± 4 42	109 1 ± 4 55	105 7 ± 2 66
81 4 ± 5 13	79 0 ± 6 38	79 0 ± 4 19
0 341 ± 0 022	0 332 ± 0 025	0 329 ± 0 022
320 9 ± 8 49	321 8 ± 7 09	318 2 ± 9 22
40 0 ± 0 32	40 0 ± 0 10	40 0 ± 0 25
108 9 ± 2 27	111 0 ± 2 51	119 5 ± 3 72
81 0 ± 2 98	80 0 ± 4 12	76 0 ± 2 37
0 343 ± 0 018	0 338 ± 0 021	0 330 ± 0 019
322 1 ± 8 51	322 7 ± 6 14	325 8 ± 12 21
41 0 ± 0 97	39 0 ± 0 98	40 0 ± 0 25
118 4 ± 4 90	122 0 ± 4 58	137 4 ± 6 17
75 0 ± 4 04	73 0 ± 3 90	66 0 ± 2 69
0 325 ± 0 024	0 323 ± 0 023	0 304 ± 0 017
326 0 ± 7 00	323 5 ± 7 00	331 8 ± 11 59
41 0 ± 0 70	41 0 ± 0 60	41 0 ± 0 39

for the pulse transmission time were not plotted for each subject

Discussion

Directional responses in all results were as expected for upright ergometer exercise increased HR and ET_c decreased PEP and PEP/LVET and stable PTT[4,5,11] With the exception of HR the time course of such changes has hitherto been reported only on a minute to minute basis

Two striking results emerge from this investigation as evidenced in the beat to beat plot (1) the *immediacy* of the changes in cardiac events at the virtual onset of exercise and (2) that these abrupt initial changes represented the *major* response to exercise during the entire minute—even over the range of workloads—in the sense that *any further* changes were gradual

Immediate responsiveness of HR to exercise has already been reported with its rapidity attributable to neural effects particularly to immediate withdrawal of vagal dominance[1,3] This mechanism was also likely to have effected the concomitant abrupt changes in STI observed in this study The decrease in PEP and increase in ET_c (which implies increased stroke volume[4,12,19]) may be attributed in part to adrenergic influences[13] Any increase in stroke volume could be partly the result of an improved ejection fraction due to the inotropic effect of adrenergic stimulation The observed decrease in PEP/LVET is consistent with such improved contractility[15] In addition both the decrease in PEP and suggested increase in stroke volume could also be due to a Frank Starling effect resulting from increased venous return In this connection Guyton and co workers[16] have shown instantaneous increase in cardiac output in areflexic dogs due to translocation of blood into the heart from the very onset of muscular exertion Moreover Rushmer and co workers[17,18] have demonstrated that cardiac stroke excursions can increase within the next heart beat after exercise begins

Finally although the work loads affected most responses later in the observation period (Figs 1 through 4) it is clear that the abruptness of the changes in all parameters was not influenced by the level of exertion

Summary

Immediate cardiac responses to exercise were investigated in five normal male volunteer subjects by measuring heart rate and systolic intervals from rest through the onset of exertion at three different work loads Recordings were continued for fifty beats and again at one minute with measurements plotted on a beat to beat basis and grouped for statistical analysis During exercise heart rate and corrected ejection time increased pre ejection period and PEP/LVET decreased and pulse transmission time remained stable The heart rate acceleration was sudden occurring in the first few beats of exercise a phenomenon also demonstrated by previous investigators A significant new finding was the *equally abrupt* major change in each of the other parameters The immediacy of all responses was independent of load and was consistent with experimental studies showing that changes in both

Table I Mean values and standard errors for HR and systolic indices during rest and one minute of exercise

Variable	*Control*	*a*	*b*	*c*
50 Watts				
Heart rate (beats/min)				
Mean ± S E	74 2 ± 2 45	100 1 ± 3 65	104 4 ± 3 48	104 6 ± 4 48
Pre ejection period (msec)				
Mean ± S E	121 ± 2 51	99 ± 5 22	94 ± 4 94	87.5 ± 5.28
PEP/LVET				
Mean ± S E.	0 486 ± 0 004	0 398 ± 0 021	0 390 ± 0 021	0 365 ± 0 023
Corrected ejection time				
Mean ± S E	275 5 ± 1 61	322 6 ± 5 09	319 2 ± 6 39	315 7 ± 7 09
PTT (msec)				
Mean ± S E	40 0 ± 4 15	40 0 ± 0 53	40 0 ± 0 13	40 0 ± 0 10
100 Watts				
Heart rate (beats/min)				
Mean ± S E	75 0 ± 2 88	96 4 ± 2 30	106 8 ± 1 78	108 4 ± 1 78
Pre ejection period (msec)				
Mean ± S E	121 0 ± 2 38	95 0 ± 2 60	93 0 ± 2 99	88 0 ± 2 78
PEP/LVET				
Mean ± S E	0 483 ± 0 004	0 379 ± 0 006	0 383 ± 0 014	0 366 ± 0 016
Corrected ejection time				
Mean ± S E	282 5 ± 3 30	318 5 ± 8 78	323 6 ± 8 56	325 0 ± 9 67
PTT (msec)				
Mean ± S E	39 0 ± 3 62	43 0 ± 2 50	42 0 ± 1 38	41 0 ± 1 30
150 Watts				
Heart rate (beats/min)				
Mean ± S E	78 7 ± 3 39	105 5 ± 4 91	113 6 ± 2 99	116 7 ± 3 75
Pre ejection period (msec)				
Mean ± S E	120 0 ± 1 82	95 0 ± 3 83	91 0 ± 3 55	81 0 ± 3 40
PEP/LVET				
Mean ± S E	0 486 ± 0 010	0 377 ± 0 018	0 382 ± 0 019	0 344 ± 0 020
Corrected ejection time				
Mean ± S E	281 6 ± 1 60	333 6 ± 7 03	329 3 ± 8 62	331 3 ± 9 20
PTT (msec)				
Mean ± S E	39 0 ± 2 66	40 0 ± 0 20	40 0 ± 0 20	41 0 ± 0 89

of the first minute increases were directly related to load

Pre ejection period (PEP Table I Fig 2) Overall similarities in initial PEP response were present at all three workloads The control periods differed significantly from a sharply decreased PEP in the first segment (A) of exercise (p < 0 01) The actual decrease (−22 to −26 msec) was virtually identical among work loads Fig 2 demonstrates the immediacy of this large decrease—i e , it occurred within the first measured beats of exercise

Following the sharp immediate drop there were additional but gradual decreases in PEP the magnitude of which appeared to be related to the load

PEP/LVET (Table I Fig 3) The single largest *decrease in* the PEP/LVET occurred from control to the first segment of exercise in all three workloads (p < 0 01) and was similar in magnitude among the loads Fig 3 indicates that this decrease occurs at the onset, i e , the beginning of segment A The last segment of exercise (E) and the one minute segment did not differ significantly among any of the workloads

Corrected ejection time (ET_c Table I Fig 4) ET increased abruptly with the onset of exercise at all three workloads At each load this increase was statistically different from the control period (p < 0 01) However, ET_c remained at the increased level for each respective workload throughout the course of exercise

Pulse transmission time (PTT Table I) The PTT for all three workloads showed no statistical difference between the control period and any segments of exercise Hence the individual beats

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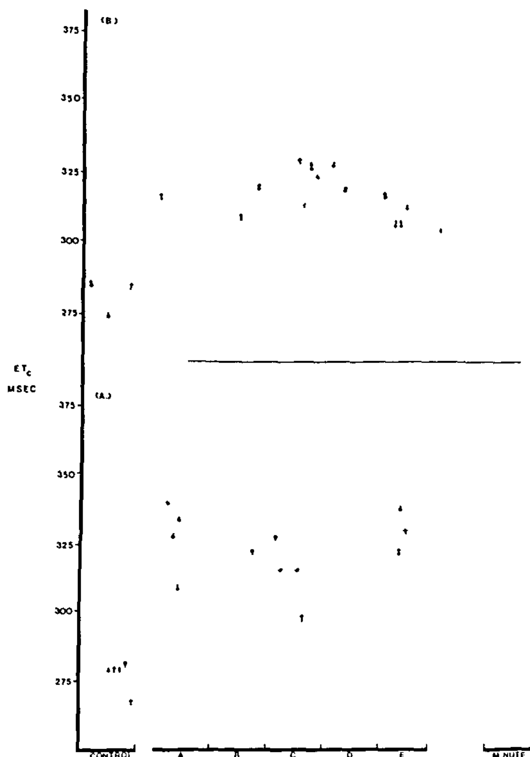


Fig 4 Beat to beat plot of corrected ejection time of five subjects at *A 50 watts B 150 watts*. For explanation of abscissa segments A to E and significance of underscoring *see text* first paragraph under Results.

neural activity and venous return at the onset of exercise are virtually instantaneous

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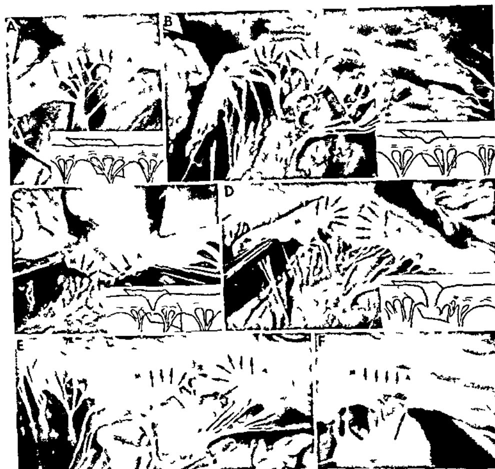


Fig 1 View from right side of heart with tricuspid valve cut open to reveal parts of right atrium and ventricle A spectrum of variations in attachment of anterior (*A*) and medial (*M*) leaflets of the tricuspid valve to the membranous ventricular septum is illustrated in *A* to *E* *A*, in 58 out of the 95 specimens a straight annulus of the tricuspid valve bisected the membranous ventricular septum (arrow) and the anterior and medial leaflets had fused to form an uninterrupted annulus. *B* in 18 specimens there was a shallow depression of the right tricuspid annulus (arrows) toward the apex of the right ventricle *C* in four specimens the valve annulus (arrows) at the commissure between the anterior and medial leaflets of the tricuspid valve was more extensively depressed and tightly bound to the membranous ventricular septum than in the specimen shown in *B* but was not interrupted, as in *D* and *E* *D* and *E* in 15 specimens the commissure between the anterior and medial leaflets of the tricuspid valve was absent at the center of the membranous ventricular septum In the specimen shown in *E* a tiny pocket of valve tissue (asterisk) remained along what would have been the valve annulus isolated from the annular attachment (arrows) of the medial and anterior leaflets of the valve *F* in this specimen, the medial portion of the anterior leaflet of the tricuspid valve was attached directly to the septal band along the normal line of attachment for chordae tendineae (lower arrow right) The commissure between the anterior and medial leaflets (upper arrows) was otherwise normally formed.

missure between the anterior and medial leaflets The tricuspid valve was absent for as little as 1 mm or as much as 7 mm the thickness of the MeVS was not increased in these specimens and there were no landmarks dividing the atrial from the ventricular portions of the MeVS at this point. In one specimen a tiny pocket of valve tissue remained along the interrupted portion of the tricuspid annulus (Fig 1 *E*) Valve regurgitation was prevented in these 15 cases by pockets of anterior and medial valve tissue (Fig 1 *D*) that were attached to the MeVS on each side of the space where the commissure had failed to form. These two pockets were anchored by chordae or a membrane to the ventricular septum and septal band. From all appearances in systole these pockets ballooned into the empty space at the MeVS to completely close the valve

Normal variations in tricuspid valve attachments to the membranous ventricular septum a clue to the etiology of left ventricle-to-right atrial communication

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In ventricular septal defect (VSD) associated with left ventricle to right atrial communication the anterior and medial leaflets of the tricuspid valve do not meet to form a normal commissure [1,2] Shunting from left ventricle into right atrium is present because there is either absence or abnormal development of the tricuspid valve leaflets adjacent to the VSD In view of this we have studied the normal relationship of the tricuspid valve to the membranous ventricular septum (MeVS) and found that 39 per cent of normal specimens comprise a spectrum in which the anteroseptal commissure of the tricuspid valve is incompletely attached to the MeVS It is suggested that when this spectrum is superimposed upon VSD left ventricle to right atrial communication might result in some of the hearts

Materials and methods

The tricuspid valve attachments to the membranous ventricular septum were defined in 95 normal hearts from the pathology collection of the Johns Hopkins Hospital (age range newborn to 70 years) These specimens are also the subjects of a detailed anatomic study of the membranous ventricular septum [3,4]

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Results

In 58 specimens (61 per cent) the tricuspid valve annulus crossed the MeVS as a straight line (Fig 1 *A*) In 39 of these 58 cases there was a raphe at right angles to the annulus of the tricuspid valve beneath the commissure In two specimens the raphe was continuous with the anterior leaflet of the tricuspid valve which was attached without chordae directly to the septal band along the normal line of attachment for chordae tendineae (Fig 1 *F*)

Thirty seven of the specimens (39 per cent) comprised a spectrum in which the anteromedial commissure of the tricuspid valve was incompletely attached to the MeVS At one end of the spectum were 18 specimens in which the annulus of the anteromedial commissure was deviated toward the apex of the right ventricle at the center of the MeVS thus making its atrial portion slightly larger at the expense of its ventricular portion (Fig 1 *B*) A raphe under this depression in the annulus supported the underside of the commissure between the anterior and medial leaflets of the tricuspid valve in all cases

In four specimens the depression was so deep and the commissure so tightly bound to the MeVS that the valve almost appeared to be interrupted (Fig 1 *C*) Here also there was a small raphé that supported the underside of the narrow commissure between the anterior and medial leaflets

In the 15 specimens at the other end of the spectrum the valve was interrupted at the center of the MeVS (Fig 1 *D*) and there was no com

Experimental and laboratory reports

Inotropic effects of tolbutamide in man

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The cardiac effects of the sulfonylurea compounds particularly tolbutamide have become the subject of considerable debate Much of this interest has been spurred by the results of long term studies which reported an increased incidence of cardiovascular deaths in diabetic patients treated with tolbutamide [1-3] Positive inotropic effects of tolbutamide and other sulfonylureas can be demonstrated in vitro[4, 5, 7] however subsequent investigations in vivo have provided conflicting results [6-9]

Inotropic agents increase myocardial oxygen demand[10, 11] and can increase the size of experimental myocardial infarctions [12] The increased incidence of coronary artery disease in the diabetic population might make them particularly prone to hazard from these effects

This study was designed to document both the degree and time course of positive inotropic effects of tolbutamide in man as measured by the noninvasive technique of systolic time intervals (STI)

Methods

Studies were carried out on six normal men aged 21 to 26 with normal fasting blood sugar and normal cardiovascular status as assessed by history physical examination and electrocardiogram Informed consent was obtained All studies were done in a quiet room with the subjects fasting and supine allowing at least three days between studies Subjects received either 1 000 mg of tolbutamide 250 mg of tolbutamide or an equivalent volume of normal saline in a random balanced design to eliminate order effect Subjects did not know which substance was being given

Twenty minutes after introduction of an intravenous line and a cannula for blood sampling in the opposite arm three baseline recordings for measurement of STI were made at 10 minute intervals The test substance was then infused over 30 seconds and recordings were made each minute for the first 10 minutes and at 15 30 60 and 90 minutes Arterial blood pressure was measured concomitantly by the brachial cuff method Heparinized blood samples were obtained at 0 2 4 6 8 10 15 30 60 and 90 minutes and analyzed for glucose insulin [13] and tolbutamide [14] Dextrose (10 per cent) was infused continously at rates of 100 mg per minute on control days and variable rates of 100 to 300 mg per minute on days when tolbutamide was given in an attempt to keep blood sugar levels constant

Simultaneous electrocardiograms phonocardiograms and carotid pulse tracings were obtained using an Elema Schonander Mingograf system at a paper speed of 100 mm per second.[15] From these recordings total electromechanical systole (QS2) left ventricular ejection time (LVET) pre ejection phase (PEP) and heart rate (HR) were obtained. PEP LVET and QS2 corrected for heart rate (PEP_I $LVET_I$ and $QS2_I$) were calculated using the regression equations of Weissler [16]

Measurements were facilitated by the use of an

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Discussion

Absence of tricuspid leaflet tissue where the annulus crossed the MeVS was noted in three of 50 (6 per cent) normal specimens studied by Silver and co workers[5] a figure considerably less than that noted in our specimens (16 per cent) Although these authors described anatomic variations of the chordae tendineae supporting the anteroseptal commissure, they did not note a spectrum of attachment of the valve to the MeVS

In early embryonic development, the com missure between the anterior and medial leaflets of the tricuspid valve forms when the dextrodor sal conus swelling[6] or right bulbar ridge[7 8] fuses with the atrioventricular cushions[6] or right tu bercles of the atrioventricular cushions[7 8] If these fused mesenchymal structures remain closely associated with the MeVS and become normally undermined during systole, the an teromedial commissure of the tricuspid valve becomes an uninterrupted expanse of valve tissue supported at the MeVS by chordae and usually a raphe and the annulus continues in a straight line across the center of the MeVS In terference with this developmental mechanism results in a spectrum of anatomic variations At one end of the spectrum is the interrupted tri cuspid annulus In intermediate steps of the spec trum the anlage for anterior and medial leaflets fuse but are not undermined sufficiently to pro duce a free margin of the valve and the com missure becomes bound down to the MeVS to a variable degree The least affected hearts have only a slight apical deviation of the valve annulus where it crosses the MeVS

These variations in the normal relationship of the MeVS to the anteromedial commissure of the tricuspid valve may have clinical significance When the secondary interventricular foramen fails to close and a VSD results those individuals with an interrupted tricuspid valve (16 per cent of our specimens) or a valve that is bound down to the MeVS (4 per cent of our specimens) could con ceivably have either a form of left ventricle to right atrial shunt or the potential for such a shunt because the VSD would not be entirely covered by valve tissue Those individuals with an uninterrupted annulus and valve mechanism would have interventricular shunts

Summary

In 39 out of 95 normal specimens there was either no commissure between the anterior and medial leaflets of the tricuspid valve, which re sulted in an interrupted valve margin at the center of the membranous ventricular septum or an incompletely formed commissure It is sug gested that one end of this spectrum of normal anatomic variations could have a direct relation ship to VSD associated with left ventricle to right atrial communication

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quate measure of inotropic response to catechol amines[20, 21] Shortening of the $QS2_I$ has been shown to be the most sensitive noninvasive parameter for detecting inotropic effects of digitalis glycosides[23, 22]

For purposes of analysis the results of the serial STI were divided into three periods In the early period (one to four minutes) peak levels of tolbutamide were attained, and glucose was constant During the intermediate period (five to 10 minutes) peak levels of tolbutamide were maintained, peak levels of insulin were attained, and glucose was constant. During the late period (15 to 90 minutes) tolbutamide and insulin levels gradually declined and glucose fell (1 000 mg dose only)

Early period (one to four minutes) No significant change occurred in $QS2_I$ or PEP_I.

Intermediate period (five to 10 minutes) PEP_I decreased by approximately 5 msec as compared to the control day (Fig 1) At no time was there a significant difference between changes produced by 1 000 vs 250 mg of tolbutamide $QS2_I$ shortening gave similar results, being in the range of 5 to 10 msec shorter than the control day Again no difference was observed between the two doses of tolbutamide

Late period (15 to 90 minutes) Both PEP_I and $QS2_I$ remained significantly below control day values through 30 minutes but rose to approach control at 60 and 90 minutes Despite glucose values significantly lower than control in this phase for tolbutamide 1 Gm and no significant change in glucose with the 250 mg dose the STI values for the two doses remained highly similar

When the data were examined by comparison only to the baseline values obtained on the same day of each intervention (Table II) changes were less noticeable and statistical significance was achieved less consistently This was primarily due to the fact that PEP_I and $QS2_I$ consistently rose during the control day thus making shortening of these intervals on the experimental days more apparent

PEP uncorrected for rate and PEP/LVET were also analyzed, and results were not different from the assessment of PEP_I No significant changes occurred in LVET or $LVET_I$ Heart rate and blood pressure remained constant

Isoproterenol (Fig 2) produced significant shortening ($p < 0.005$) of the PEP_I at a dose of only 0 2 μg Response was linearly related to log

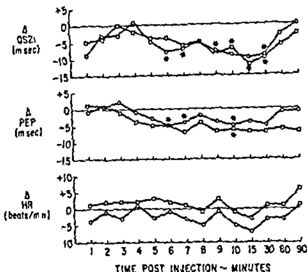


Fig 1 Mean deviation from saline control (Δ) of PEP_I $QS2_I$ and heart rate after tolbutamide (O = 250 mg □ = 1 000 mg) For abbreviations see text.

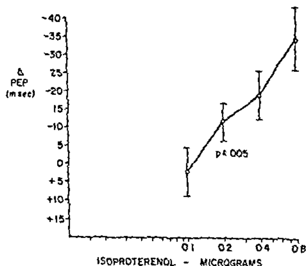


Fig 2 Dose—response curve isoproterenol

dose as has been observed previously for PEP[21, 20]

Discussion

Although tolbutamide and other sulfonylureas have been found to activate myocardial adenyl cyclase[26] and have a positive inotropic effect on various in vitro preparations from experimental animals[4, 5, 7] studies on human papillary muscle function[5] and in vivo studies have been less convincing In the intact dog Guzman Pinakatt and Yeh[6] found that 16 mg per kilogram of intravenous tolbutamide produced transient (two minutes) and small (approximately 10 per cent)

Table I Serial glucose, insulin, and tolbutamide levels (mean ± S D)

	Time (minutes)									
	0	2	4	6	8	10	15	30	60	90
Glucose (mg/100 ml)										
Control	107 ± 7	106 ± 6	108 ± 9	105 ± 6	108 ± 9	108 ± 9	110 ± 9	108 ± 11	109 ± 16	108 ± 17
250 T	112 ± 8	112 ± 8	112 ± 8	112 ± 10	112 ± 8	111 ± 10	113 ± 12	108 ± 13	115 ± 15	114 ± 16
1 000 T	110 ± 11	108 ± 11	109 ± 11	107 ± 9	105 ± 5	107 ± 11	101 ± 14	80 ± 25*	75 ± 16	83 ± 7
Insulin (ng/ml)										
250 T	3 4 ± 2 5	4 1 ± 2 5	5 9 ± 1 8	8 5 ± 4 4	8 1 ± 2 0	8 3 ± 3 0	6 9 ± 3 5	5 9 ± 3 2	6 1 ± 3 4	5 3 ± 1 4
1 000 T	4 7 ± 1 7	5 4 ± 2 1	7 0 ± 3 9	8 6 ± 1 1	9 2 ± 4 0	7 6 ± 2 5	7 2 ± 1 6	6 0 ± 1 4	5 5 ± 1 4	5 0 ± 2 2
Tolbutamide (mcg/ml)										
250 T	0	44 ± 41	49 ± 23	42 ± 18	46 ± 18	35 ± 12	32 ± 9	32 ± 15	30 ± 11	25 ± 9
1 000 T	0	98 ± 62	144 ± 59	135 ± 36	158 ± 38	153 ± 33	144 ± 22	132 ± 21	131 ± 38	105 ± 23

p< 0 05 (comparison to control values)

electronic digitizing table (Computer Equipment Corporation Model PF 10C Pencil Follower) having a nominal mechanical resolution of 0 1 mm Coordinates of fiducial marks of each tracing were also digitized to provide internal calibration Results were recorded on magnetic tape and analyzed by computer which calculated the STI, averaged the collected data over 7 to 10 cycles depending on heart rate and punched the data on cards for later analysis This method results in "blinding' for practical purposes since the observer has no idea of the results being obtained at the time of measurement The method was checked for accuracy against tracings previously measured by hand Individual measurements of QS2 and LVET were all within 5 msec and the means for five cycles were all within 3 msec , the average difference between means for a study being 1 msec In our hands this method of reading STI resulted in a fourfold decrease in tracing analysis time

STI results were analyzed as follows values for each time were compared to the mean of the subject s three baseline values for that day, and the mean deviation from baseline tabulated for either control tolbutamide 250 mg or tolbutamide 1,000 mg In addition, changes from baseline produced by tolbutamide were compared to changes at the respective time after injection on the saline control day for each patient The significance of the changes from baseline on each day and from the control infusion were assessed by Student's t test for paired observations

Isoproterenol sensitivity testing was carried out on a separate day on each individual to serve as a positive control Sequential intravenous boluses of isoproterenol were given until a heart rate increase of at least 25 beats per minute was achieved, and dose response curves were constructed This method, as performed in our laboratory has been described previously[17] At the point of maximal chronotropic effect (shortest three R R intervals) STI were obtained using the five cycles bracketing these three

Results

Serial glucose insulin, and tolbutamide levels are recorded in Table I Glucose levels remained constant throughout the control day and constant values were also maintained after administration of tolbutamide 250 mg Adjustments in dextrose administration were inadequate to prevent a statistically significant fall in glucose levels at 15 30 60, and 90 minutes in the subjects given tolbutamide, 1,000 mg but levels were stable during the first 10 minutes of these studies

Insulin reached peak values between six and 10 minutes in patients receiving tolbutamide and slowly declined thereafter remaining above baseline levels after 90 minutes No significant difference was noted between insulin levels after 250 or 1 000 mg of tolbutamide

Tolbutamide levels were approximately fourfold higher with the 1 000 mg dose Levels peaked early and gradually declined, consistent with the known half life of the drug of four to six hours[18]

Shortening of the $QS2_I$ and PEP_I were used as indices of inotropic effect Changes in PEP accurately reflect changes in isovolumic contraction time[19] and have been considered to be an ade

of the drug itself It is of interest however that although no significant drop in blood sugar occurred with 250 mg of tolbutamide the deviations from baseline remained essentially the same as with 1 000 mg tolbutamide

No evidence for a positive *chronotropic* effect of tolbutamide was found in this study nor have any other studies in intact animals or man revealed this

In a recent preliminary communication Crockett and co workers[9] found no significant change in PEPi or QS2i after 1 000 mg of intravenous tolbutamide in four normal control subjects These patients were assessed only at 5 15 and 30 minutes after infusion and no control infusion was carried out Our results are generally in agreement with this as almost no discernible difference was noted until patients were compared to their own saline control

Our positive results were obtained by frequent monitoring of STI and utilization of appropriate controls Nevertheless changes seen were small in relation to the dose of the drug employed, and of borderline statistical significance There was no evidence of a dose response relationship for tolbutamide and changes temporally coincided with peak insulin levels The mechanism of these minor inotropic effects remains speculative but could be a direct effect of insulin or conceivably an insulin induced increase in substrate availability for myocardial energy metabolism Even if the small changes noted could be clearly attributed to tolbutamide their significance in regards to morbidity and mortality of diabetic patients would remain questionable While inotropic agents given during the course of an acute myocardial infarction can extend injury there is no direct evidence to date that a chronic, mild, positive inotropic effect is harmful In fact an increase in cardiovascular mortality similar to that seen with tolbutamide has been noted among diabetic patients taking phenformin[3,4] an agent which has no inotropic effects[4] Thus it would appear that the small changes produced by tolbutamide on the heart are unlikely to be clinically significant and other effects must be sought to explain the reported excess cardiovascular mortality

Summary

The hemodynamic responses of normal subjects to intravenous injections of tolbutamide 250 mg and 1 000 mg were assessed by measurements of serial systolic time intervals

Analysis of results compared to saline control revealed evidence of minor inotropic effects during the period five to 10 minutes after infusion Small but statistically significant ($p < 0.05$) decreases in pre ejection phase and electromechanical systole were noted. The time response of these changes did not correlate with dose or blood level of tolbutamide and appeared to coincide with peak insulin levels

No inotropic or chronotropic effects were seen during the first four minutes after infusion suggesting that the myocardial adenyl cyclase stimulating properties of the drug previously demonstrated in vitro are not significant in intact man The minor late inotropic effects are of doubtful clinical significance and cannot be invoked to explain the reported increased cardiovascular mortality of patients treated with tolbutamide

We thank Marie Nieberding R N for technical help and Pfizer Laboratories for assaying plasma tolbutamide

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Table II Changes (Δ) from mean baseline with time after injection of tolbutamide

		Control													
		Time (min.) after injection													
Parameters	*Baseline*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*15*	*30*	*60*	*90*
Saline															
PEPi (msec)	136	1	−1	0	2	2	2	3	2	4	5	7	7*	8	9
± S D	12	2	3	3	3	3	2	4	6	5	2	3	4	5	6
QS2i (msec)	545	5	1	1	−1	0	1	2	4	4	5	9	7*	8	5
± S D	16	6	6	8	4	7	9	5	4	6	5	7	6	6	9
Tolbutamide 250 mg															
PEPi (msec)	140	0	0	2	1	−1	−3	−2	0	0	0	3	2	7	8
± S D	9	5	2	5	5	4	4	3	5	4	4	5	10	7	7
QS2i (msec)	550	−4	−2	−2	0	−5	−7	−5	−1	−4	−4	−1	−2	5	5
± S D	14	7	4	4	4	4	7	5	6	7	5	5	11	8	7
Tolbutamide 1 000 mg															
PEPi (msec)	132	2	0	−1	−2	−3	−3	−4	−2	−3	−1	0	0	2	2
± S D	14	7	2	4	4	3	5	4	3	2	2	6	6	10	3
QS2i (msec)	541	0	−3	1	−3	−4	−3	−4	−2	−5	−2	−3	−3	2	2
± S D	20	7	7	8	9	5	5	5	6	4	4	4	4	7	5

Indicates significant difference (P < 0 05) from baseline For abbreviations see text.

increases in left ventricular dp/dt, however, Constantine and McShane[7] noted no effects with doses up to 30 mg per kilogram of intravenous tolbutamide or chlorpropamide Tolbutamide binding to protein in vivo has been suggested as an explanation for the discrepancy between in vitro and in vivo results[24 25]

Our data fail to support a prominent direct inotropic effect of tolbutamide in man No change occurred in PEPi or QS2i during the first four minutes after infusion of the tolbutamide bolus whereas catecholamines, thought to act by adenyl cyclase activation,[27] produce peak effects within one minute when infused in a similar manner

Statistically significant effects, however were seen during the intermediate period after infusion (five to 10 minutes) These changes might have been due to tolbutamide but correlated more closely with the period of peak insulin levels In addition, despite a fourfold difference in tolbutamide levels with the two doses insulin levels were the same, and changes in systolic time intervals were essentially the same Recently, insulin itself has been shown to exert inotropic effects in vitro in the absence of substrate[28] The effects seen during this period, (Fig 1) though significant were small (PEPi decreased approximately 5 msec QS2i decreased approximately 8 msec) Isoproterenol (Fig 2) by comparison, decreased PEPi 11 msec at a dose of only 0 2 mcg ($p < 0.005$) and 18 msec at a dose of 0 4 mcg Data from the literature reveal a 15 msec fall in QS2i with deslanoside 0 4 mg intravenously[29]

Other studies in intact humans have given conflicting results Hildner[8] administered 250 mg of tolbutamide intravenously to patients at the time of cardiac catheterization, and noted shortening of the PEP and lowering of left ventricular end diastolic pressure but no change in cardiac index or systolic pressure Others however found no significant change in STI after 1 000 mg of intravenous tolbutamide[9]

In our study, care was taken to prevent a fall in plasma glucose levels by titrating infusions of dextrose Nevertheless, significant drops in glucose levels occurred at 15 and 60 minutes with the 1 Gm dose Little information is available on glucose levels in earlier studies in humans[8] Hypoglycemia is known to be associated with an increase in adrenergic activity[30 31] and increased plasma levels of glucagon[32] Both epinephrine and glucagon have pronounced inotropic effects which can easily be measured by systolic time intervals[20 33] (Epinephrine infused at 5 mcg per minute produced a mean decrease in PEP of 30 msec glucagon given in bolus doses of 50 mcg per kilogram decreased PEP 13 msec)

For these reasons we separated our results of 15 and 60 minutes and did not consider them in our interpretation of the possible inotropic effect

Late hemodynamic results of fascia lata reconstruction of the right ventricular outlet

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The surgical correction of persistent truncus arteriosus most cases of complete transposition with ventricular septal defect and pulmonary stenosis and extreme tetralogy of Fallot all require construction or reconstruction of the right ventricular outflow tract A number of materials have been advocated for this purpose with apparently sati factory immediate results [1-4] However for how long will they remain satisfactorv? Aortic homografts frequently undergo calcification of the aortic tube and mild systolic gradients across the valve are common [1,5] Severe stenosis due to calcification of the homograft valve has been described in two cases to date [6,7]

This paper looks at the long term performance of autologous fascia lata in the right ventricular outflow tract

Materials and methods

Eight patients who had undergone reconstruction of the right ventricular outflow tract with autologous fascia lata as previously described[3,8] were recatheterized at intervals from 1 2 to 2 4 years postoperatively Immediately after cardiopulmonary bypass the maximum pressure gradient across the fascial valve was 15 mm Hg and no murmurs of pulmonary incompetence were heard in the early postoperative period Table I details the original diagnosis and age at operation in each patient In the one patient (No 5) with pulmonary atresia and ventricular septal defect a bypass conduit graft[3] consisting of a tube containing a tricuspid fascial valve had been used whereas in the remainder a shorter diamond shaped graft tube[3] containing a tricuspid fascial valve had been inserted into the right ventricular outflow tract Informed consent to recatheterization was obtained from each patient or his parents and all patients resident in England who had survived operation were reinvestigated, regardless of symptoms or the results of clinical examination

Right heart catheterization was carried out in the fasting state after premedication with 1 ml per 20 pounds of a mixture containing 25 mg of pethidine 6 25 mg of chlorpromazine and 6 25 mg of promethazine HCl per milliliter (maximum adult dose 2 5 ml) Resting cardiac output was measured by the direct Fick method, with the flow through method being used for oxygen consumption [9] In three children investigated prior to the development of this method oxygen uptake was assumed [10] An attempt to assess the degree of pulmonary regurgitation by cine angiography was made in five patients with injection of contrast medium into the main pulmonary artery This proved difficult because of the invariable extreme mobility of the catheter the tip of which in many cases lay in the distal right pulmonary artery during systole and fell back into the right ventricle during diastole That this should occur with a relatively stiff NIH catheter is in itself suggestive of quite severe pulmonary regurgitation Rapid biplane Elema right ventriculograms were performed in all but two patients

Results

Clinical findings All patients were asymptomatic and required no medication They were acyanotic and in sinus rhythm In every case

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Fig 1 *A* Patient 5 Lateral view of selective right ventricular angiocardiogram six weeks after insertion of bypass graft Infundibular pulmonary atresia was present though the right ventricular outflow tract has opacified. The bypass graft tube functions well and the fascial valve cusps (white arrows) which were fully mobile are shown in diastole Origin of fascial tube marked with black arrows



Fig 1 *B* Patient 5 Same view fifteen months postoperatively The fascial tube is slightly narrower and also shorter The valve cusps have shortened and thickened, now forming no more than projections into the conduit (white arrows) The pulmonary arteries have enlarged postoperatively Origin of fascial tube marked with black arrows

Those patients with diamond shaped composite grafts were not reinvestigated in the early postoperative phase By the time recatheterization had been carried out no fascial cusp mobility was demonstrable in any patient The fascial tube was easily differentiated from right ventricular myocardium by its absence of trabeculation The fascial valve was defined in the frontal plane in only one patient but in the lateral view there was invariably an abnormality visible at the site of the fascial valve ring This took the form either of an abrupt concentric or eccentric stenosis of the fascial tube itself (Figs 2 and 3) or else a thick more or less straight diaphragm across the tube In one patient (No 6) free tricuspid regurgitation was also demonstrated.

Operative findings Re operation has been carried out in five of the patients so far [1,3,6,8] In each case the graft tube was functioning satisfactorily but at the site of the valve, no leaflets whatever were visible and the orifice of the fascial tube narrowed abruptly to between 6 and 10 mm in diameter There was no obstruction to right ventricular outflow at the anastomosis of the graft with either the right ventricle or the pulmonary artery The composite fascia lata graft was replaced with one of preserved heterologous pericardium containing a monocusp valve [11] Two patients had small residual ventricular septal defects (1 to 3 mm in diameter) which were repaired, and in one patient the papillary muscle of the conus which had been detached at the original operation resulting in tricuspid incompetence was re attached to the septum Each patient survived and the results have so far been satisfactory

Discussion

When continuity between the right ventricle and pulmonary artery must be created *de novo* in conditions such as persistent truncus arteriosus

Table I Clinical material

Patient No.	Original diagnosis	Age at operation (years)
1	DORV with PS	12
2	Fallot s tetralogy	9
3	Fallot s tetralogy	15
4	PVS (hypoplastic annulus)	22
5	Pulmonary atresia + VSD	6
6	Fallot s tetralogy	9
7	DORV with PS	32
8	Fallot s tetralogy	9

DORV with PS = double outlet right ventricle with pulmonary stenosis PVS = pulmonary valve stenosis and VSD = ventricular septal defect

Table II Hemodynamic data

Patient No	Pressures (mm. Hg)				Cardiac output (L./min./M²)
	RA(a)	RV	PA	FA	
1	8	124/4	20/5	110/70	3 4
2	8	160/8	18/7	100/70	2 9
3	6	80/3	20/5	100/75	2 6
4	cv = 10	80/10	25/10	130/70	2 0
5	13	102/6	21/3	109/58	3 4
6	cv = 11	90/5	20/4	118/76	2 7
7	14	100/7	32/10	135/75	2 8
8	16	115/13	28/8	94/54	3 1

cv = right atrial cv wave FA = femoral artery PA = pulmonary artery RA (a) = right atrial a wave and RV = right ventricle

there was elevation of the jugular venous pressure, with the a wave dominant in every patient except Patient 6 who had a cv wave of tricuspid incompetence A left parasternal lift was present in all but one patient varying from slight to marked, and a systolic thrill was invariably present in the second or third intercostal space at the left sternal border On auscultation a loud ejection systolic murmur was audible in the pulmonary area in each case and there was a pansystolic murmur in the patient (No 6) with tricuspid regurgitation The pulmonary component of the second heart sound was inaudible in three patients and very soft in the remainder, and in every case but one (Patient 6) there was a low pitched decrescendo diastolic murmur immediately after the pulmonary component The interval between A_2 and P_2 or the onset of the diastolic murmur was wide and varied a little with inspiration The electrocardiogram showed complete right bundle branch block in six patients (associated with left axis deviation in one) and right ventricular hypertrophy in two patients Chest roentgenography revealed cardiothoracic ratios of between 0 50 and 0 65, but otherwise no striking abnormality

Hemodynamic data The results of cardiac catheterization are summarized in Table II Resting cardiac output ranged between 2 0 and 3 4 L. per minute per square meter (mean 2 9) The right ventricular end diastolic pressure ranged from 4 to 13 mm Hg and the right atrial a wave was correspondingly elevated In two patients (Nos 4 and 6) the right atrial pressure trace was suggestive of tricuspid regurgitation The right ventricular systolic pressure varied between 80 and 160 mm Hg (mean 106 mm Hg) and was higher than the simultaneous femoral artery pressure in two patients Systolic pressure gradients between the right ventricle and pulmonary artery ranged from 55 to 142 mm Hg (mean 83 mm Hg) The end diastolic pressures in the right ventricle and pulmonary artery were within 5 mm Hg of each other in every case There was no oximetric evidence of any residual intracardiac shunt

Statistical correlations were sought between the right ventricular systolic pressure the time interval between operation and recatheterization the right ventricular end diastolic pressure the height of the right atrial a wave and the cardiothoracic ratio, but none of significance was found

Angiocardiography Selective right ventricular angiocardiography had been carried out in one patient (No 5) with a bypass graft six weeks postoperatively and had demonstrated thickened, but freely mobile fascial valve cusps (Fig 1 A) At this time the right ventricular systolic pressure was 80 mm Hg When this patient was catheterized again 16 months after operation the right ventricular systolic pressure had risen to 102 mm Hg and there had been some diminution in diameter of the entire tube of fascia lata The most striking change however was in the fascial leaflets which had shrunk and thickened to immobile nubbins of tissue (Fig 1, B)

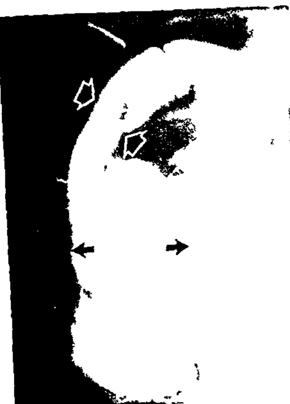


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the study has served to emphasize how important late hemodynamic studies of conduits of this type are even in asymptomatic patients

Summary

Eight patients were catheterized between 1 2 and 2 4 years after reconstruction of the right ventricular outflow tract with autologous fascia lata Whereas the immediate post bypass pressures had demonstrated a maximum gradient of 15 mm Hg across the fascial valve at the time of recatheterization this varied from 55 to 142 mm Hg (mean 83 mm Hg) Right ventricular systolic pressure varied between 80 and 160 mm Hg (mean 106 mm Hg) All but one patient had clinical *evidence of pulmonary incompetence*

Selective angiocardiography with injection into the right ventricle and pulmonary artery demonstrated shrunken thickened immobile valve cusps with an abrupt stenosis of the fascial tube or a diaphragm across it

Re operation has been done in five patients In each the graft tube functioned satisfactorily, but at the site of the valve no leaflets were visible and the orifice of the conduit narrowed abruptly to 6 to 10 mm in diameter

It is concluded that autologous fascia lata is unsuitable for reconstruction of the right ventricular outflow tract

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Fig 2 Patient 6 Lateral view selective right ventricular angiocardiogram sixteen months after insertion of diamond shaped conduit There is eccentric stenosis of the fascial tube originating mainly posteriorly The fascial cusps (white ar rows) are tiny and immobile Origin of fascial tube marked with black arrows There is also considerable tricuspid regurgitation.



Fig 3 Patient 8 Lateral view selective right ventricular angiocardiogram fifteen months after insertion of diamond shaped tube graft There is concentric gradual narrowing of the fascial tube maximal at the site of the tiny immobile valve cusps (white arrows) Origin of fascial tubes marked with black arrows

and congenital pulmonary atresia the necessity of using a conduit containing a valve is well es tablished A more difficult decision has to be made in those cases of Fallot s tetralogy and dou ble outlet right ventricle with pulmonary steno sis where relief of pulmonary stenosis can only be achieved at the cost of destroying the pulmonary valve by inserting a patch across its annulus

Though the symptomatic results up to five years after outflow tract patching with pericar dium are excellent there is no doubt that the postoperative cardiothoracic ratio is higher in patients with patches than without so that the long term fate of this type of repair remains in question [12] Therefore the search for a satisfacto ry competent pulmonary valve replacement in tetralogy is a legitimate one *Some reservations* about the long term value of autologous fascia lata in the right ventricular outlet have already been expressed by us [6] and Ross and Somerville[13] reported two patients with severe right heart failure within a year of this type of operation

Prior to surgical correction the patients we have described had all had severe symptoms which were completely relieved by operation Despite this, cardiac catheterization in all availa ble survivors has demonstrated that late obstruc tion of the fascial valve invariably occurs togeth er with the development of valve regurgitation The findings at reoperation indicate that this happens because of shortening thickening and fusion of the fascial cusps together with shrinkage of the fascial tube at the point where the valve has been inserted We have not estab lished with certainty whether this change occurs fairly rapidly and then remains static or whether it is gradually progressive However two observa tions suggest that the major changes occurred *within the first postoperative year* First in one patient the immediate postbypass right ventricu lar systolic pressure was 45 mm Hg whereas at six weeks postoperatively it was 80 mm Hg and at 15 months 102 mm Hg Second we were una ble to correlate postoperative interval with right ventricular systolic pressure or fascial valve gra dient in the definitive study performed 1 2 to 2 4 years postoperatively

Because of these disappointing results we no longer use or recommend autologous fascia lata in the right ventricular outflow tract However

ventricular ejection time Third the isometric contraction time as determined by echocardiography calculated as the interval from the onset of systolic closure of the mitral valve (the *B point*) to aortic closure sound less left ventricular ejection time (the ultrasonically derived isometric contraction time) (Fig 1)

The internal isometric contraction time was measured during cardiac catheterization from the left ventricular the aortic pressure curves and the ECG in 11 patients using a saline filled manometer In three patients the mitral echogram and the phonocardiogram were recorded simultaneously with the left ventricular pressure curves using a high fidelity catheter tip manometer (Statham SF1) The internal isometric contraction time calculated as the interval from the onset of rise of left ventricular pressure to the point when aortic diastolic pressure is reached [2]

All the intervals were measured to the nearest 5 msec At least five cardiac cycles were used in the calculations during which the patient was breathing normally The intervals were corrected for heart rate using the indices of Weissler Harris and Schoenfeld [3] All the patients were well stabilized on their respective therapy and no changes in drug treatment were carried out until the time of cardiac catheterization which was performed one to three days subsequently

An ICL 4100 computer was employed for the statistical least squares correlation of invasive and noninvasive data One tail tests of significance were used. Student s t test was performed with two tail tests of significance

Results

The results from the ten normal subjects are shown in Table I The results from the patients group are shown in Table II The isometric contraction time as measured by the ultrasound method showed an excellent correlation with the *internally recorded* isometric contraction time (r = 0 92 P < 0 01) (Fig 2) The external isometric contraction time correlated at only the 50 per cent level with the internal isometric contraction time and was significantly shorter than the internal isometric contraction time (P < 0 01)

The isometric contraction time as determined by ultrasound method discriminated well between the normal group and the group of patients (P < 0 01) while with the external iso

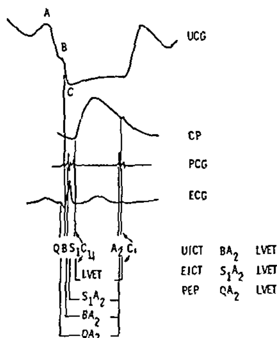


Fig 1 A schematic illustration of the methods used to measure the isometric contraction time externally Ci carotid incisura Cp external carotid pulse tracing Cu carotid upstroke ECG electrocardiogram EICT external isometric contraction time LVET left ventricular ejection time PCG phonocardiogram PEP pre-ejection period UCG ultrasound of the mitral valve *and UICT* ultrasound *isometric contraction time*

Table I Measurements of external isometric contraction time pre ejection period and ultrasonically isometric contraction time in normal subjects

No.	*Age*	*EICT*	*PEP*	*UICT*
1	24	32	92	43
2	21	31	94	52
3	23	54	97	79
4	21	31	63	48
5	26	44	101	56
6	52	59	105	78
7	40	58	100	61
8	45	43	85	57
9	28	41	93	57
10	27	46	98	62
Mean		43 9	92 8	59.3
S D		10 6	11 8	11 6
S E M		3 4	3 7	3 7

All values in milliseconds.
EICT = external isometric contraction time
PEP = pre-ejection period.
S D = standard deviation.
S E.M = standard error of the mean
UICT = ultrasonically measured isometric contraction time

The use of echocardiography to measure isometric contraction time

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An important approach to the quantification of the contractile state of the left ventricle has been the study of the rate at which intraventricular pressure rises or the first derivative of ventricular pressure dp/dt As the main determinant of the duration of the isometric contraction time is the peak dp/dt[1] hence the importance of estimating this time accurately None of the current methods available for estimating the isometric contraction time is satisfactory In this paper, we discuss some of the currently available techniques and suggest an alternative method of estimating the isometric contraction time using echocardiography

Methods

Twenty five subjects were studied Fifteen patients with primary myocardial disorders and *ischemic heart disease and 10 normal subjects* The normal subjects were volunteers from the staff of the hospital None of them had symptoms or signs of heart disease and their chest radiograph and electrocardiograms (ECG s) were normal Five were males and five were females Their ages ranged between 21 and 52 years with a mean of 30 7 years Five patients had hypertrophic cardiomyopathy Their ages ranged from 15 to 52 years Six patients had congestive cardiomyopathy their ages ranged from 22 to 51 years Four patients had ischemic heart disease aged 38 to 67 years All the patients had cardiac catheterization and left ventricular angiography Coronary arteriography was performed in the group of patients with congestive cardiomyopathy and ischemic heart disease

All the patients had a simultaneous recording of the external carotid pulse phonocardiogram an electrocardiographic lead and a mitral echogram For the recording a 6 channel Cambridge Scientific Instruments (Type 72112) machine was employed The position of the phonomicrophone (suction microphone, Type 72352) was chosen so as to display clearly the first high frequency vibrations of the first heart sound (M_1) and the aortic component of the second heart sound The filter band was ± 3 dB from 25 Hz to 1 KHz (manufacturers specifications) The carotid pulse was recorded over the right carotid artery using *a funnel connected by polyethylene tubing to* a piezo electric transducer connected to a pulse amplifier (Cambridge Type 72354) with a frequency response of ± 3 dB 0 1 Hz to 100 Hz and a time constant 1 6 second An external ECG lead was chosen which showed clearly the onset of ventricular depolarization as a reference lead

The mitral echogram was recorded using an Ultrasonoscope (Smith and Kline Eskoline 20) connected to the Cambridge machine The photographic paper speed was set at 100 mm per second From the recordings three intervals were measured First the external isometric contraction time calculated as the interval from the first high frequency vibrations of the first heart sound to the aortic component of the second heart sound less left ventricular ejection time Second the pre ejection period calculated as the interval from the beginning of the QRS complex of the ECG to the aortic closure sound less left

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Discussion

The isometric contraction time is the interval from the onset of left ventricular contraction to the opening of the aortic valve.[4] The main determinant of the duration of the isometric contraction time is the rate of rise of pressure within the left ventricle (dp/dt).[1,5] Other factors include the end diastolic pressure of the left ventricle and the aortic diastolic pressure. Various methods have been suggested to measure the duration of the isometric contraction time. Having access to direct pressure tracings, isometric contraction time can be calculated from the point when the left ventricular pressure starts to rise to the point when the aortic diastolic pressure is reached. Braunwald, Fishman and Cournand[6] have reported average values for the isometric contraction time in patients without cardiac disability recorded directly during thoracotomy. For an isometric contraction time starting with the onset of left ventricular pressure rise their average value was 61 ± 12.1 msec, the average pre ejection period was 115 ± 11.7 and the Q onset of left ventricular systole 52 ± 6.7 msec. These values are useful for comparison with indirect methods, although techniques using the onset of subendocardial and papillary muscle contraction as a starting point for the isometric contraction time would tend to give higher values.[7] Apart from certain technical and physiologic objections to the direct method, it cannot be repeated serially, hence the need for easily derived, repeatable noninvasive methods unaccompanied by procedural hazards to the patients. The mitral component of the first heart sound has been taken to represent the onset of isometric contraction. Several objections have been raised to the use of this method. It is doubtful whether the first high frequency vibrations of the first heart sound represent in actual fact the mitral valve closure.[8,9] Mitral valve closure is not completed until left ventricular contraction has already started. From the technical point of view, the mitral component of the first heart sound may be difficult or impossible to identify with certainty. Furthermore the first high frequency vibrations of the first heart sound bear no constant relationship to the onset of left ventricular isometric contraction.[10] The average normal value in the present study, however, is in good agreement with those reported by other workers.[2,11]

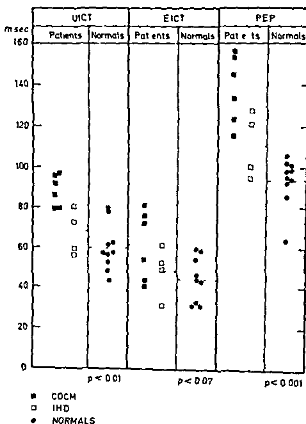


Fig. 3. A comparison of the duration in milliseconds of the ultrasonically determined isometric contraction time (UICT), external isometric contraction time (EICT), and pre-ejection period (PEP) in normal subjects and in patients with congestive cardiomyopathy (COCM) and ischemic heart disease (IHD).

The pre ejection period comprises the electrical depolarization time, electro mechanical coupling, and the isometric contraction time. The former two have not been observed to vary during physiologic and pharmacologic maneuvers. Variation in the pre ejection period in a single subject should therefore reflect changes in isometric contraction time.[2] However, the isometric contraction time cannot be directly deduced from the pre ejection period because of individual variations in the duration of its other components.

Also the pre ejection period cannot be used in patients with complete left bundle branch block or with hemiblock.[12,13] It has been shown that the pre ejection period is prolonged in patients with left bundle branch block in the absence of left ventricular functional impairment.[14]

The onset of the upstroke of the apex cardiogram may reflect the earliest inception of

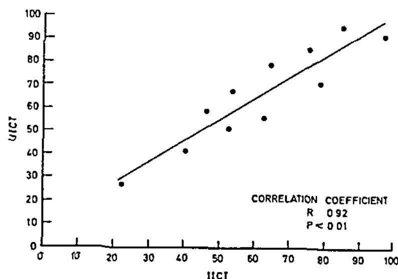


Fig 2 The least square relationship between the ultrasonically determined isometric contraction time (UICT) and the internally determined one (IICT) The measurements are recorded in milliseconds

Table II Measurements of internal isometric contraction time ultrasound isometric contraction time external isometric contraction time and pre ejection period in patients group

No	*Diagnosis*	*IICT*	*UICT*	*EICT*	*PEP*
1	HOCM	53	68	53	104
2	HOCM	40	42	28	96
3	HOCM	22	27	16	60
4	HOCM	52	52	42	122
5	HOCM	—	41	31	81
Mean		41 7	46 0	34 0	92 6
6	COCM	96	92	54	113
7	COCM	75	86	72	156
8	COCM	—	79	41	123
9	COCM	64	79	43	115
10	COCM	—	95	76	154
11	COCM	84	96	81	145
Mean		79 7	87 8	61 2	137 7
12	IHD	—	80	61	120
13	IHD	62	56	31	94
14	IHD	46	59	49	100
15	IHD	78	72	52	127
Mean		62 0	66 7	48 2	110 2

All values in milliseconds
COCM = congestive cardiomyopathy
EICT = external isometric contraction time
HOCM = hypertrophic obstructive cardiomyopathy
IHD = ischemic heart disease
PEP = pre ejection period
IICT = internally determined isometric contraction time
UICT = ultrasound determined isometric contraction time

metric contraction time the results were not significant *The pre ejection period also showed* significant difference between the normal and the patients values (P < *0 001) (Fig 3)* Taking all the subjects as one group the external isometric contraction time was found to be significantly shorter than the ultrasound measured isometric contraction time (P < 0 001) and also shorter than the internal isometric contraction time (P < 0 01)

The simultaneous recording of the mitral *echogram and the left ventricular* pressure curves using a catheter tip manometer showed that the B point of the mitral echogram coincides exactly with the onset of left ventricular contraction (Fig 4)

ject one day to another Sometimes the B point is not well identified but if the transducer beam is directed toward a point between the edge of the valve and the mitral annulus the B point will usually be clearly seen The B point is often more evident in patients with an abnormally functioning left ventricle than in patients with a normally functioning left ventricle or in normal individuals[20] We tested the time relationship of the B point with the onset of isometric contraction of the left ventricle in three patients by simultaneously recording the mitral echogram with the left ventricular pressure curves as recorded through a catheter tip manometer (Fig 4) We found in these patients that the B point coincided with the onset of rise of left ventricular pressure curve In the eleven patients in whom we recorded the internal isometric contraction time during cardiac catheterization an excellent correlation was found between the internally measured and the ultrasonically measured isometric contraction time (Fig 2) The mean isometric contraction time as measured by the ultrasound method was found to be 5 7 msec longer than the internal isometric contraction time

Although the difference was not significant this was not an unexpected finding because the internally recorded isometric contraction time in this study was calculated from pressure curves obtained through saline filled manometer with an inherent delay in the system

The earliest onset of systole contraction of the papillary muscles and the subendocardial myocardial layer does not give rise to an appreciable elevation in intracavitary pressure and considerable deep intramuscular pressure rise has been recorded in dogs[7] before the left ventricular pressure starts to rise

One of the limitations of the method of using the ultrasound is the fact that a satisfactory mitral echogram with a clear B point may take considerable time to obtain This applies especially to normal people in whom the mitral valve leaflets are thin and move very fast Nevertheless it appears from this study that the isometric contraction time as measured by the ultrasound method is a convenient sensitive and physiologic method to measure the isometric contraction time It is well suited for bedside evaluation of patients with myocardial disease and their differentiation from normal subjects It seems superior to the external isometric contraction time and it does not have the disadvantage of the pre ejection period of containing components unrelated to the mechanical contractile process It can also be used in the presence of left ventricular conduction disturbances It is not susceptible to variations inherent in data obtained during cardiac catheterization due to physiologic psychologic and pharmacologic stress to which the patients have to adapt It can be repeated serially especially to evaluate the progress of disease or to study the effect of pharmacologic agents and the response to a special form of therapy Although it is more difficult to record than the other noninvasive methods it is a convenient and reliable parameter of cardiac function

Summary

The current methods for estimating isometric contraction time were discussed Ultrasonically derived isometric contraction time using external carotid pulse tracing phonocardiogram and the B point of the mitral echogram was also measured. Recordings were performed in 10 normal subjects and 16 patients Hypertrophic cardiomyopathy (5) congestive cardiomyopathy (6) and ischemic heart disease (4) In 11 patients, the results were correlated with the internal isometric contraction time The ultrasound isometric contraction time showed good correlation with the internal isometric contraction time ($r = 0\ 92$ $P < 0\ 01$)

The external isometric contraction time showed less correlation with the internal *isometric contraction time and was significantly* shorter ($P < 0\ 01$) The ultrasound isometric contraction time showed a superior discriminating value to the external isometric contraction time for differentiating the normal subjects from the patients group

We are grateful to Professor J F Goodwin and Dr C M Oakley for their great help and advice and also to Dr D J Coltart for his assistance in reviewing the manuscript

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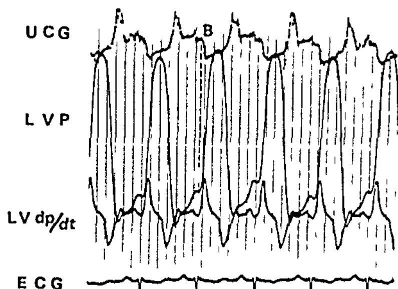


Fig 4 The simultaneous recording of the mitral echogram (UCG) left ventricular pressure using a manometer tipped catheter (LVP) Lv dp/dt and electrocardiographic lead The B point of the mitral echogram coincides exactly with the onset of left ventricular pressure rise

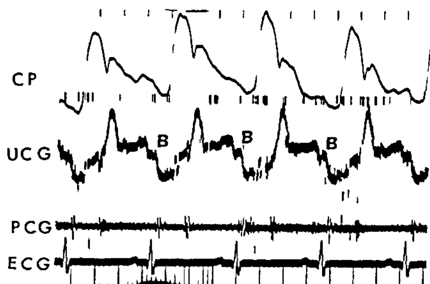


Fig 5 The simultaneous recording of the external carotid pulse curve (CP) mitral echogram (UCG) phonocardiogram (PCG) and electrocardiographic lead from a patient with congestive cardiomyopathy The B point of the mitral echogram is well defined

systole [15] This point is usually defined with confidence in normal subjects but may be difficult to determine in patients with heart diseases Spodick and Kumar[16] felt that this method fulfilled their criteria in their study of normal subjects However, wide variations in the type of tracings illustrated in reports from various laboratories, and difficulties in obtaining satisfactory records in patients with thick chest walls obesity, emphysema, and some types of heart diseases have made this method somewhat less than ideal [9 17 18]

The normal mitral echogram was described by Edler [19] With the onset of ventricular diastole the anterior leaflet of the mitral valve moves rapidly anteriorly to a sharp peak the E point following this rapid valve opening the anterior leaflets move posteriorly or toward a closed position After some minor oscillations during diastole the valve opens again following atrial contraction At the onset of systole the curve falls abruptly forming segment B C as designated by Edler (Fig 5) The B point forms a shelf on the closing downstroke of the mitral valve echo We have found it to be constant and reproducible from one subject to another and in the same sub

Relationship of pulmonary artery diastolic and pulmonary artery wedge pressures in mitral stenosis

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The relationship between pulmonary artery diastolic pressure and mean pulmonary artery wedge pressure in normal man has been reported by various investigators[1,2] The diastolic pressure gradients across the pulmonary vascular bed in congenital heart disease with left to right shunt, in acquired valvular heart disease and in coronary heart disease have also been studied[3,4] Harvey and Enson[5] in reviewing the literature noted a few observations on the pulmonary artery diastolic and pulmonary artery wedge pressures in patients with mitral stenosis However no correlation between these two pressures was attempted in these patients Herein we report our observations on the relationship between these two pressures at rest and during exercise in patients with mitral stenosis and normal pulmonary vascular resistance

Material and methods

Hemodynamic studies performed in 33 patients with mitral stenosis in normal sinus rhythm with normal pulmonary vascular resistance form the basis of this report A pressure gradient of 5 mm. Hg or less between pulmonary artery diastolic and mean pulmonary artery wedge pressures at rest was taken as normal pulmonary vascular resistance The subjects comprised 14 men and 19 women aged 9 to 42 years the average being 25 years

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A right heart catheterization was performed using a No 6 or No 7 Cournand catheter Intracardiac and intravascular pressures were recorded through a Statham P23 AA transducer on an Electronics for Medicine multichannel recorder The base line for the pressure measurements was the middle of the chest at the level of the second costal cartilage with the patient in a supine position[6] After recording the resting pulmonary artery and pulmonary artery wedge pressures the catheter was placed in the pulmonary artery wedge position and the patient was given supine leg raising exercise for five minutes or until the pulmonary artery wedge pressure rose above 30 mm Hg The pulmonary artery wedge and pulmonary artery pressures were recorded while the patient was still exercising as a pull back tracing The inherent fallacy of consecutive recording in trying to estimate pressure gradients between two low pressure chambers was considered insignificant in this study All wedge positions were confirmed by oximetry and pull back tracing to the pulmonary artery

Results

The relation between pulmonary artery diastolic and mean pulmonary artery wedge pressures at rest is shown in Fig 1 Pulmonary artery diastolic pressure varied from 10 to 32 (mean 18 48 ± 5 50) mm Hg The mean pulmonary artery wedge pressure had a range of 10 to 28 (18 24 ± 4 64) mm Hg These two pressures had a correlation coefficient (r) of 0 9017 The differences between the resting pulmonary artery wedge and pulmonary artery diastolic pressures (PAW PAD) was from −5 to +4 (−0 24 ± 2 40) mm Hg (Table I)

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Table I—continued

No	Name	Age	Sex		Pulmonary artery pressure (mm. Hg) Systolic	Diastolic	Mean	PAW (Rec) (mm. Hg)	PAW PAD (Rec) (mm. Hg)	PAW (Pred.) (mm. Hg)	PAW PAW (Rec) (Pred.) (mm. Hg)
17	PD	28	F	R	68	31	49	27	−4	36	+1
				E	88	40	62	37	−3		
18	S	9	F	R	63	32	44	28	−4	32	+2
				E	73	36	55	34	−2		
19	RK	17	F	R	28	16	21	16	0	26	−1
				E	40	26	34	25	−1		
20	MG	32	M	R	37	22	29	24	+2	38	+4
				E	68	36	50	42	+6		
21	MBX	21	F	R	44	25	33	23	−2	38	+3
				E	70	40	52	41	+1		
22	JS	11	M	R	34	15	20	15	0	30	0
				E	52	30	35	30	0		
23	ABK	24	F	R	20	10	15	10	0	24	0
				E	36	24	30	24	0		
24	LW	42	F	R	38	19	27	18	−1	43	−3
				E	75	44	58	40	−4		
25	BB	25	F	R	32	20	26	18	−2	38	−2
				E	60	40	48	36	−4		
26	NS	40	M	R	36	14	24	15	+1	31	−6
				F	68	30	42	25	−5		
27	DD	28	F	R	33	18	24	17	−1	25	−2
				E	42	26	32	23	−3		
28	S	31	F	R	31	18	24	17	−1	33	−2
				E	63	34	47	35	+1		
29	MD	19	F	R	36	20	27	20	0	28	0
				E	50	28	37	28	0		
30	MG	24	M	R	23	14	17	13	−1	22	0
				E	35	23	30	22	−1		
31	SG	15	M	R	40	26	30	26	0	37	−1
				E	57	37	44	36	−1		
32	PB	30	F	R	26	16	19	16	0	31	+1
				E	54	31	42	32	+1		
33	TM	40	F	R	22	10	15	10	0	30	+2
				E	60	30	40	32	+2		

because of the nature of selection of patients (r = 0 9017) However during exercise a close correlation existed between the two pressures in the present study (r = 0 8670)

The relationship between (PAW PAD$_R$) and (PAW PAD$_E$) had a correlation coefficient (r) of 0 7995 which is highly significant The mean difference between these two measurements was only +0 15 ± 2 46 mm Hg It was therefore thought that if the exercise PAD was corrected by the difference (PAW PAD) at rest it might be a better index of PAW during exercise The correlation between the predicted exercise PAW (PAW$_{PE}$) calculated by the equation

$$(PAW_{PE}) = [(PAD_E) + (PAW\ PAD_R)]$$

and measured exercise PAW (PAW$_{ME}$) (Table I) was very close (r = 0 9561) (Fig 4) The correlation between the measured PAW and estimated PAW by the above equation was significantly higher than between the measured PAW and exercise PAD (P < 0 05)

The response of the pulmonary circulation obtained in the present study in patients with mitral stenosis and normal pulmonary vascular resistances was similar to that observed in normal subjects[1,2] Although an increase in mean pulmonary artery and pulmonary artery wedge pressures during exercise in mitral stenosis has been observed by previous workers[6,8] only a few patients with normal pulmonary vascular resistances were reported No correlation was at

Table I Pulmonary artery and pulmonary artery wedge pressures in mitral stenosis

No	Name	Age	Sex		*Pulmonary artery pressure (mm. Hg)*			*PAW (Rec) (mm Hg)*	*PAW PAD (Rec) (mm. Hg)*	*PAW (Pred.) (mm. Hg)*	*PAW PAW (Rec) (Pred.) (mm. Hg)*
					Systolic	*Diastolic*	*Mean*				
1	PP	18	M	R	39	20	23	20	0		
				E	67	34	39	32	−2	34	−2
2	RS	12	M	R	40	20	27	19	−1		
				E	56	37	43	37	0	36	+1
3	RS	24	M	R	28	12	18	14	+2		
				E	60	30	42	32	+2	32	0
4	UG	20	F	R	40	24	30	25	+1		
				E	60	34	42	36	+2	35	+1
5	VD	42	F	R	39	20	28	15	−5		
				E	48	24	35	20	−4	19	+1
6	SB	30	F	R	48	24	31	20	−4		
				E	55	27	35	22	−5	23	−1
7	M	19	F	R	21	10	14	13	+3		
				E	48	25	34	31	+6	28	+3
8	AKS	14	M	R	40	21	28	24	+3		
				E	50	25	35	30	+5	28	+2
9	AG	26	M	R	34	19	26	22	+3		
				E	77	48	59	50	+2	51	−1
10	S	35	F	R	25	11	16	14	+3		
				E	43	16	24	21	+5	19	+2
11	PK	33	M	R	30	17	22	17	0		
				E	68	40	51	40	0	40	0
12	JSJ	36	M	R	30	17	22	17	0		
				E	64	43	50	43	0	43	0
13	S	9	M	R	62	23	36	18	−5		
				E	96	44	60	32	−12	39	−7
14	SCG	23	M	R	35	15	25	13	−2		
				E	52	29	41	22	−7	27	−5
15	KLN	27	M	R	32	15	22	18	+3		
				E	58	32	41	35	+3	35	0
16	BD	24	F	R	35	15	23	19	+4		
				E	81	41	58	46	+5	45	+1

PAW (Rec) = mean pulmonary artery wedge pressure (recorded) PAW (Pred) = mean pulmonary artery wedge pressure (predicted) R = resting and E = exercise

Exercise data The relation between pulmonary artery diastolic and mean pulmonary artery wedge pressure during exercise is shown in Fig 2 The pulmonary artery diastolic pressures varied from 16 to 48 (32 85 ± 7 45) mm Hg and the pulmonary artery wedge pressures ranged from 20 to 50 (32 45 ± 7 70) mm Hg The correlation coefficient (r) between these two pressures was 0 8670 The difference between pulmonary artery wedge pressure and pulmonary artery diastolic pressure during exercise (PAW PAD) was from −12 to +6 (−0 39 ± 3 91) mm Hg

Relationship of PAW PAD in exercise and resting states The difference between the pressure gradients of PAW and PAD during exercise and at rest [(PAW PAD_E) − (PAW PAD_R)] varied from −4 to +7 (+0 15 ± 2 46) mm Hg The correlation coefficient between the (PAW PAD_R) and (PAW PAD_E) was 0 7995 (Fig 3)

Discussion

It is apparent from this study there is a close correlation between the pulmonary artery diastolic and mean pulmonary artery wedge pressures at rest and during exercise in patients with mitral stenosis and normal pulmonary vascular resistances Yu and co workers [7] reported good correlation between PAW and PAD pressures at rest (r = 0 825) in 32 patients with mitral stenosis but no exercise study was done by these workers The correlation of these pressures at rest was very high as expected

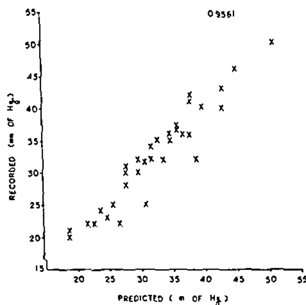


Fig 4 R lation between recorded mean pulmonary artery wedge (PAW) and predicted pulmonary artery wedge pressure during exercise

artery wedge and pulmonary artery diastolic pressures at rest (r = 0 9017) and during exercise (r = 0 8670) A method of predicting pulmonary artery wedge pressure from pulmonary artery diastolic pressure during exercise was formulated. The correlation between the predicted and measured exercise pulmonary artery wedge pressures was very close (r = 0 9561) It is suggested that during exercise the pulmonary artery diastolic pressure can be modified as above and substituted for mean pulmonary artery wedge pressure if the resting gradient between pulmonary artery wedge and pulmonary artery diastolic pressure is known.

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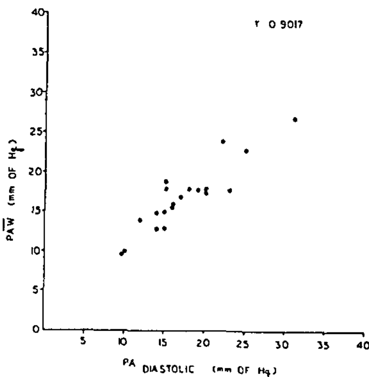


Fig 1 Relation between mean pulmonary arterial wedge (PAW) and pulmonary artery diastolic pressure (PAD) at rest.

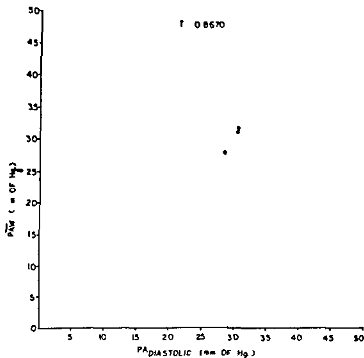


Fig 2 Relation between mean pulmonary arterial wedge (PAW) and pulmonary artery diastolic pressure (PAD) during exercise

tempted between pulmonary artery diastolic and mean pulmonary artery wedge pressures at rest and during exercise in these studies

The findings indicate that the pulmonary circulation in patients with mitral stenosis with normal pulmonary vascular resistance behaves like that in normal subjects during exercise, and

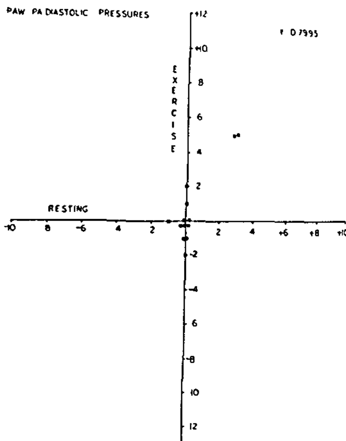


Fig 3 Relation between difference of the mean pulmonary arterial wedge (PAW) and pulmonary artery diastolic pressure (PAW PAD) at rest and during exercise

in such patients the exercise pulmonary artery diastolic pressure itself can give a good estimate of the mean pulmonary artery wedge pressure However, a closer value can be obtained by modifying the exercise pulmonary artery diastolic pressure by the equation

$$PAW\ exercise = PAD\ exercise + Resting\ (PAW - PAD)$$

This may be of practical importance in those circumstances where the reliable recording of the pulmonary artery wedge pressure pulse during exercise is not possible

Summary

Resting and exercise hemodynamic studies were performed in 33 patients with mitral stenosis (14 men and 19 women average age 25 years) in normal sinus rhythm with normal pulmonary vascular resistances A normal pulmonary vascular resistance was assumed when the resting pressure gradient between the pulmonary artery diastolic and mean pulmonary artery wedge pressures was 5 mm Hg or less A satisfactory correlation existed between the pulmonary

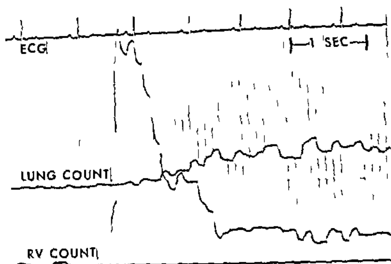


Fig 1 Radioisotope dilution curves following injection of ^{131}I MAA into the right ventricle One scintillation counter positioned over the right ventricle (RV COUNT) detects the initial rise followed by an exponential decline to a plateau. A second counter positioned over one lung (LUNG COUNT) detects the ^{131}I MAA as it is carried into the lung and is trapped in the pulmonary capillaries producing the plateau in both curves. This radioactivity from the lung as recorded by the lung count distorts the exponential down slope of the RV COUNT curve as indicated in Fig 2 ECG is the electrocardiogram

Methods

Technique and procedure In the initial series of experiments right ventricular volumes were determined in each of the 14 dogs to establish the normal variation among individuals Duplicate determinations were obtained in six of the e dogs to establish the reproducibility of the method. We also wished to know whether right ventricular function (as indicated by volumes) in a given dog remained relatively constant over a period of several weeks With this objective nine of the original 14 dogs were restudied after an interval of one month

Healthy mongrel dogs 18 9 ± 1 9 (S D) kilograms in weight were anesthetized by the intravenous administration of 10 per cent chloralose in polyethylene glycol 200 in a dosage of 65 to 100 mg per kilogram of body weight and were kept in a supine position for the duration of the experiment. Additional chloralose was administered as required. Ventilation was maintained by a volume limited re pirator (Harvard Model 607) An electrocardiogram was obtained from limb leads A polyethylene cannula was introduced into the femoral artery percutaneously according to the Seldinger technique to record the systemic blood pressure and to take blood samples A catheter with multiple holes at the tip (polyethylene or NIH 6F or 7F) was introduced into the right heart via the exposed jugular vein for the purpose of injecting dye or radioactive indicator and determination of blood pressure in the right cardiac chambers or the pulmonary artery Blood pressure was recorded with strain gauge pressure transducers (Statham P23 Db) Cardiac output was measured with the dye dilution method. Indocyanine green 2 5 mg was injected rapidly into the pulmonary artery through the catheter The concentration of dye in the arterial blood withdrawn by a pump (Harvard Model 600 910) at a speed of 19 4 ml per minute via the arterial cannula was measured continuously with a cuvette densitometer (Waters XP 250A) The blood collected during each determination was immediately reinfused into the animal P_{O_2} P_{CO_2} and pH of the arterial blood samples obtained anaerobically were determined by appropriate electrodes (Radiometer) at 38 0 C and corrected to the rectal temperature of the dog

The time activity curve of radioactive iodine labeled macro aggregated albumin (^{131} I MAA) injected into the right ventricle was recorded in the following manner One collimated scintilla

Measurement of right ventricular volumes using ^{131}I-MAA

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When the contractile properties of the myocardium remain constant then the contractile tension developed during systole is proportional to the diastolic fiber length within limits This length tension relationship when applied to the intact mammalian heart indicates that the stroke work of systole is a function of end diastolic volume provided that myocardial contractility remains unchanged This is the classical Frank Starling mechanism which determines the performance of the normal heart as a pump [5,21] Within the limits of this concept ventricular performance can be determined from measurements of end diastolic volume the subsequent stroke volume the residual or end systolic volume and the pressure generated during systole

Various indicator dilution techniques have been employed by a number of investigators to measure volumes of the left ventricle in diastole and systole Jacob and colleagues[11] and, more recently Wilckin[24] estimated left ventricular volumes in man by means of the dye dilution technique Holt[9] obtained ventricular volume measurements by employing the dye dilution method using T 1824 in combination with the electrical conductivity method with 4 per cent sodium chloride solution as the indicators Rapaport Wiegand, and Bristow[17] applied the thermodilution technique injecting either room temperature saline or cooled autologous blood into the left ventricle of the dog to estimate the residual volume Folse and Braunwald[4] employed a precordial radioactivity counting system with the intraventricular injection of ^{131}I labeled Diodrast

Few studies of right ventricular volumes have been reported Although the same methods as used for the left ventricle were applied for the right ventricle i e dye dilution [1,6] electrical conductivity [10] radioisotope dilution [2,3,13] and thermodilution [12,14,15,18] they have not been completely satisfactory because of technical difficulties resulting from the anatomic relationships of the right ventricle and the pulmonary artery In radiocardiography with RIHSA [3] for instance the down slope of the time activity curve from the right ventricle was prematurely interrupted at the time when the radioisotope appeared in the left side of the heart Consequently it was difficult to calculate an accurate value for the right ventricular volume The thermodilution method with chilled saline possibly involved a technical error due to the heat transfer between the ventricular wall and the chamber blood [19]

The purpose of this report is to describe a newly devised precordial counting method which could overcome the abovementioned difficulties in the measuring of right ventricular volumes during systole and diastole

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Table I Right ventricular volumes pressures heart rates, residual ratios and blood gases for each of 14 dogs anesthetized with Chloralose Measurements were repeated about one month later on nine of these same dogs.

No of Dog	Body wt (Kg)	ESV/EDV (%)	CO (l/min.)	HR (beat/min.)	STV (mL)	ESV (mL)	EDV (mL)	P_{PA} (mm Hg)	SW (Gm-cm.)	$P_{RV\,s/d}$ (mm Hg)	P_{Ao} (mm Hg)	PA_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pHa	Hematocrit (%)
1	20 4	41 0	2.486	188	13 3	9 2	22.5	16 0	307 9	29 0/1 0	156	68 0	32.8	7 332	45 0
2	20 4	44 6	1 329	178	7 5	7 0	14 5	12 0	132 4	30 0/0 0	140	66 0	33 0	7 292	50 0
3	15 9	39 9	1 907	187	10 2	6 8	17 0	21 0	30[illegible] 5	41 0/1 0	148	71 8	36 5	7 322	51 7
4	18 2	36.2	1 816	76	23 9	13 6	37.5	13 0	455 3	32 0/1 0	138	81 5	27 0	7 415	44 8
5	18 2	43 6	1 980	109	18 2	15 0	33 2	15 0	395 9	36 0/2 0	1[illegible]4	83 0	22.2	7 455	41 0
6	18.2	34 7	1 648	77	21 4	11 4	32 8	13 0	407 7	30 0/2 0	172	83 5	26 9	7 428	40 2
7	17 3	40 2	2.393	88	27 2	18 3	45 5	20 0	776 6	30 0/2.0	160	74 4	33 2	7 367	38 0
8	20 0	36 5	1 617	73	22 2	12 8	35 0	19 0	602 8	31 0/2 0	146	75 5	34 3	7 349	36 5
9	19 0	43 0	2.065	94	22.0	16 6	38 6	11 0	3[illegible]9 7	27 0/1 5	150	7[illegible] 8	38 7	7 358	39 0
10	16 0	41 5	1 358	120	11 3	8 0	19 3	11 0	184 8	14 0/0 5	120	90 1	24 8	7 431	38 7
11	22.7	[illegible]9 1	2.09[illegible]	86	24 4	15 7	40 1	11 0	399 0	23 0/1 5	139	73 0	34 7	7 395	33 1
12	20 0	39 7	3 328	120	27 7	18 2	45 9	11 0	4[illegible]3 0	29 0/1 5	160	82 2	33 5	7.359	37 0
13	18 2	44 8	1 315	58	22.7	18 4	41 1	13 0	432.5	23 0/2 0	120	9[illegible] 5	33 7	7 332	38 [illegible]
14	20 5	41 4	2 320	90	25 8	18.2	44 0	17.0	630 9	33 0/2 0	140	67 1	33 0	7 331	38 0
Mean	18 9	40 4	1 976	110	19 8	13 5	33 4	14 5	417 4	29 1/1 4	146	78 0	31 6	7 369	40 8
±1 S.D	+1.9	±3 1	±0 548	±44	±6 6	±4 4	±10 8	±3 5	±170 0	±6 4±0 7	±15	±9 4	±4 9	±0 048	±5 2
One month later															
1	19 5	35 1	2 437	190	12 8	6 9	19 7	17 0	313 0	34 0/0 5	160	81 8	27 5	7 378	44 5
2	19 1	41 8	1 700	116	14 7	10 6	25 3	11 0	240 4	28 5/1 0	148	66 0	23 0	7 395	47 0
3	16 8	38 4	1 579	113	14 0	8 7	22 7	14 0	284 9	31 0 1 0	146	68 9	22 0	7 400	49 0
4	18 2	37 0	2 172	72	30 2	17 7	47 9	17 0	738 4	37 0/3 0	154	88 0	19 3	7 553	46 5
5	18 6	33 1	1 938	74	26 2	13 0	39 2	15 0	569 9	3[illegible] 0/1.5	148	81 7	27 5	7 410	40 0
6	18 6	44 4	2 165	102	21 2	16 9	38 1	1 0	461 1	29 0/2 5	162	76 5	35 6	7 306	45 0
7	17 3	35 9	1 792	96	18 7	10 4	29 1	16 0	433 0	36 0/1 0	158	77 0	31 5	7 365	45 0
8	19 5	40 8	2.010	69	29 1	20 1	49 2	16 0	673 [illegible]	35 0/1 5	176	60 0	44 6	7 325	44 0
9	17 7	33 1	1 283	51	25 2	12 4	37 6	10 0	3[illegible]6 8	21 0/2 0	142	75 5	28 9	7 406	37 0
Mean	18 4	37 7	1 897	98	21 3	13 0	34 3	14 6	454 6	31 5/1 [illegible]	155	77 3	28 9	7 398	44 3
±1 S.D	+1 0	±3 9	±0 350	±41	±6 7	±4 4	±10 7	±2 5	±174 3	±4 9±0 8	±10	±[illegible]5	±7 7	±0 0[illegible]2	±3 7

ESV/EDV = re dual ratio CO cardiac tput, HR = h art rate StV stroke olume ESV = end sy toli volume EDV = end d astolic volume P_{PA} = mean pulmonary arterial pressure SW = stroke work, PRVs/d = right entri ular end systolic and end diastoli pressure P_{FA} = mean femoral arterial pressure Pa_{O_2} = arterial oxygen tension Pa_{CO_2} = arterial carbon dio d tension pH = arterial pH

detector will see a smaller amount of lung tissue To adjust for these differences in the absolute levels of radioactivity in the final plateaus the two plateaus are equated to 100 per cent It is then possible to correct the precordial washout curve by subtracting from it a per cent of its final plateau equal to the simultaneously recorded per cent of the final plateau in the lung When this is done and the corrected washout curve is plotted semilogarithmically the resulting down slope becomes linear (Fig 2) It is the slope λ of this corrected curve which is then used to calculate the residual ratio

Results

A typical radioisotope dilution curve detected by the precordial scintillation counter following the instantaneous injection of [131]I MAA into the right ventricle is illustrated in Fig 1 The exponential gradient λ determined from the corrected semilogarithmic plot of this curve was 1 278 which gives a residual ratio (ESV/EDV) of 0 402 i e the residual or end systolic volume calculated by using λ was 40 2 per cent of the end diastolic volume Since the stroke volume calculated from the cardiac output measured simultaneously by the dye dilution method was 27 2 ml in this dog the calculated ESV was 18 3 ml and the EDV was 45 5 ml

The data for each animal obtained by this method are presented and summarized in Table I The residual ratio of the right ventricle was 40 4 ± 3 1 (S D) per cent and the stroke volume was 19 8 ± 6 6 ml Calculated ESV was then

tion detector was positioned almost perpendicularly above the sternum at a distance of 2 5 cm from the skin so that the aperture of the collimator pointed to the center of the right ventricular area determined by an x ray film taken previously A second detector was positioned over the lung field against a side wall of the chest horizontally to record the build up curve from the lung Approximately 100 microcuries of ^{131}I MAA in a volume of 0 3 to 0 5 ml was injected into the right ventricle followed with 5 ml of saline in less than 1 0 second through the multiholed catheter tip (which had been withdrawn into the right ventricle from the pulmonary artery immediately after the measurement of cardiac output) The simultaneous time activity curves from the right ventricle and the lung field were recorded at a chart speed of 50 mm per second (Fig 1) All of the records were made on a multichannel photographic oscillograph (Electronics for Medicine)

The detectors employed in this study were scintillation counters containing a thallium activated sodium iodide crystal 1 inch by 1 inch fitted with a brass collimator slightly tapered 3 cm in diameter with an aperture depth of 7 cm beyond the crystal (Picker) The photomultipliers of both scintillation detectors were led into the count rate meter with the time constant set at 0 1 second and a scale selection of 1 000 counts per minute The output of the rate meter was directly proportional to the radioactivity detected and was led to the direct current (DC) preamplifier of the recorder

Calculations According to the indicator dilution principle if a known amount of radioactive indicator is injected rapidly into the right ventricular cavity and the time activity curve is recorded by means of a scintillation counter placed over the precordium the disappearance course of the indicator from the ventricle will be an exponential function of time indicating the amount of isotope remaining in the ventricular blood at the end of each cardiac cycle However the random disintegration of isotope and the time constant of the rate meter make it impossible to record this process in an exponential steplike fashion on the time activity curve The down slope therefore is simply assumed to be an exponential curve and the following formula is applied to calculate the right ventricular residual ratio

$$ESV/EDV = e^{\lambda \frac{t}{N}}$$

where ESV is the end systolic volume EDV is the end diastolic volume ESV/EDV is the ventricular residual ratio (Appendix A) λ is the slope of the straight line obtained by replotting the down slope of the time activity curve of the radioisotope on a semilogarithmic graph (Appendix B), t is an arbitrarily selected time interval in seconds and N is the number of the heart beats in the period of t seconds

Therefore $\frac{t}{N}$ is equivalent to the average R R interval in seconds on the electrocardiogram

The fractions of right ventricular volume were then calculated according to Holt [9] and the stroke work according to Holland and Klein [8] as follows

$$EDV = \frac{StV}{1 - ESV/EDV}$$

$$ESV = EDV - StV$$

$$SW = StV \times P_{\overline{PA}} + \frac{\rho\ StV\ V^2}{2G}$$

where StV is forward stroke volume in milliliters SW is stroke work for the right ventricle in grams centimeters $P_{\overline{PA}}$ is mean pulmonary arterial pressure in centimeters of water ρ is density of blood V is velocity of ejection in centimeters per second and G is the gravitational constant

It was observed that the majority of the time activity curves when replotted semilogarithmically deviated upward from a simple exponential in the latter part of the curve (Fig 2) owing to the radioactivity which accumulated in that portion of the lung which intervened between the counter and the heart In order to obtain the true exponential curve from the heart exclusively it was necessary to subtract the lung build up curve from the ventricular time activity curve graphically Once the ^{131}I MAA has been trapped in the pulmonary capillary bed the radioactivity recorded by both the precordial and the lung detectors reaches a stable plateau It is assumed that the MAA is distributed uniformly throughout the lung i e, that the radioactivity per unit of lung tissue is uniform However the total absolute radioactivity recorded by each detector will be dependent upon the volume of lung tissue seen by that detector By intent the precordial

the right ventricle ejects approximately 60 per cent of its EDV over the entire range of EDV observed in this group of dogs

Constancy of right ventricular function In nine dogs the initial study was followed by a second study one month later Even if ventricular function remained constant absolute volumes would be duplicated only if the ventricle happened to be operating at the same point on its normal function curve Such a coincidence was improbable and so it is more meaningful to examine the relationship between StV and EDV when comparing the two studies on each dog Fig 5 illustrates that the ventricular function curve which describes the original population of 14 dogs also describes the behavior of each individual dog when observed at two different times In other words when a given dog is studied under similar experimental conditions his right ventricular function appears to remain relatively constant over an extended period of time

In general then the variations in EDV observed in these dogs result from variations in the factors which normally determine EDV and the Frank Starling mechanism then accounts for the resulting variations in stroke volume ESV and stroke work

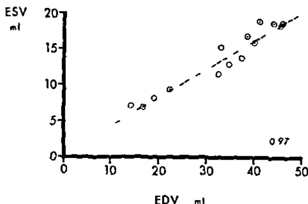


Fig 4 Since the right ventricle normally ejects a constant fraction of its end diastolic volume (EDV) then the larger the EDV the greater the volume of blood remaining at the end of systole (ESV) The data from 14 individual dogs indicate this constancy of the residual ratio (ESV/EDV) at 40 4 ± 3 1 per cent

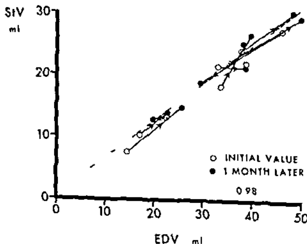


Fig 5 Nine of the 14 dogs studied initially were restudied one month later The dependence of stroke volume (StV) on end diastolic volume (EDV) observed initially in Fig 3 (open circles) was again demonstrated in the second study (closed circles) These data indicate that right ventricular function remains relatively constant over a period of one month

Discussion

Comparison with data obtained by other methods For the purpose of estimating the residual blood volume of the right ventricle the dye dilution method was employed first by Bing Heimbecker and Falholt[1] and more recently by Freis Rivara and Gilmore[6] Freis Rivara and Gilmore[6] reported the residual ratio to be 46 5 ± 5 4 per cent in man injecting indocyanine green into the right ventricle while sampling from the pulmonary artery This method however had an inherent potential error due to incomplete mixing of the dye with the ventricular blood and distortion of the time concentration curve owing to the laminar flow in the sampling catheters[9, 16] Moreover the necessity of introducing two catheters limited the clinical application

Donato and co workers[2, 3, 13] employing the radioisotope dilution method, reported the right ventricular residual ratio to be 57 5 ± 3 8 per cent in man As Rapaport and co workers[18] indicated, however it appeared that sometimes the injection of RIHSA was not made into the right ventricle but into the right atrium Furthermore the exponential down slope of the dilution curve which was required for precise calculation of the residual ratio tended to be interrupted with early overlapping of the radioisotope activity appearing from the left side of the heart and the lungs More recently Rapaport and associates[18] reported a residual ratio of 53 4 ± 10 9 per cent by the thermodilution technique in man With this method Rolett Sherman and Gorlin[19] indicated the possibility of a technical error which might have resulted from heat transfer between the ventricular wall and the chamber blood together

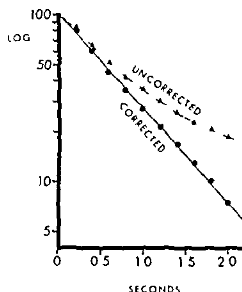


Fig 2 When the down slope of the RV COUNT curve from Fig 1 is replotted semilogarithmically (triangles) the resulting uncorrected curve is not linear due to distortion by radioactivity from the lung. This distortion is removed by subtracting the lung count (see text). The resulting corrected curve (closed circles) is linear and its slope is then used to calculate the residual ratio

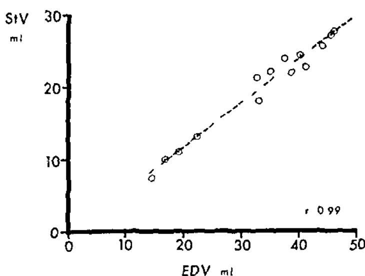


Fig 3 The dependence of stroke volume (StV) on end diastolic volume (EDV) in keeping with the Frank Starling mechanism. One data point from each of 14 individual dogs

13.5 ± 4.4 ml and the corresponding EDV was 33.4 ± 10.8 ml. Heart rate was 110 ± 44 beats per minute. Other parameters, i.e., pulmonary and systemic arterial pressures, cardiac output, hematocrit and arterial blood gases were as expected for dogs under chloralose anesthesia. Since these studies were performed in Denver at 1,600 meters of altitude where P_B is 630 mm Hg and P_{IO} is 120 mm Hg, the Pa_{O_2} of 78 mm Hg is also normal.

Reproducibility Duplicate isotope dilution curves were obtained in rapid succession in six additional experiments while the heart rate remained unchanged either with or without atrial pacing. The results (Table II) indicate that the reproducibility of the determination of the residual ratio is excellent.

Table II Reproducibility of duplicate residual ratio determinations

Dog No	*First (%)*	*Second (%)*	*Difference*
8	40.8	40.3	−0.5
9	33.1	33.8	0.7
12	39.7	38.4	1.3
13	55.1	55.1	0
14	42.2	42.2	0
15	48.5	49.2	0.7
			Mean = −0.07 SD ±0.6

Variation in volumes among individuals Under conditions of chloralose anesthesia with normal blood oxygenation and normal blood pH, the range in EDV was 17.0 to 49.2 ml. Right ventricular EDV is highly correlated with right ventricular end diastolic (filling) pressure (r = 0.77) suggesting that variations in filling pressure among individuals account for much of the variation in EDV within the group. The duration of diastole will also influence EDV as indicated by the negative correlation between heart rate and EDV (r = −0.77). Hence individual differences in heart rate also contribute to the group variation in EDV.

Since all dogs were studied under similar conditions, then to the extent that their myocardial contractile state was also similar, the Frank Starling mechanism should express the relationship between EDV and stroke volume. This was remarkably true for these group data as seen in Fig 3. Mean pulmonary arterial pressure (P_{PA}) was normal in all animals and therefore stroke volume was the major determinant of stroke work. Consequently, right ventricular stroke work was also highly correlated with EDV (r = 0.79) for this group of dogs.

Even though stroke volume increased with increasing EDV, there was also an increase in residual ESV (Fig 4). Consequently, the residual ratio tended to remain constant at 40.4 ± 3.1 as indicated by the minimal variation in the slope (ESV/EDV) of the data in Fig 4. In other words

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Appendix A

Calculation of the ventricular residual ratio ESV/EDV from the isotope indicator washout curve where ESV = end systolic volume and EDV = end diastolic volume

If the indicator were injected into the ventricle during diastole with complete and instantaneous mixing then

$$C = \frac{I}{EDV} \qquad C_1 = \frac{I_1}{ESV}$$

where I = quantity of indicator in the ventricle
C = concentration of indicator in the ventricle
a = end diastolic phase
a+1 = subsequent end systolic phase

Since the concentration of indicator remains constant from diastole through the subsequent systole

$$C = C_{+1}$$

$$\frac{I}{EDV} = \frac{I_1}{ESV}$$

$$\frac{ESV}{EDV} = \frac{I_{+1}}{I}$$

This same general relationship applies throughout a series of consecutive cardiac cycles from beat number a through beat number n

with a long sensor time constant In human studies by Sekimoto (unpublished observations) employing ^{131}I MAA and precordial counting, the residual ratio of the right ventricle was 56 2 ± 6 5 per cent in five normal individuals

With regard to experiments on dogs Holt and Allensworth[10] applied the electrical conductivity method with concentrated salt solution as an indicator injected into the right ventricle to obtain the time conductivity record of the blood in the pulmonary artery using a double lumen electrical conductivity catheter They determined the residual ratio to be 57 0 ± 14 6 per cent in seven dogs The major disadvantage of this method, as Goodwin and Sapirstein[7] indicated was that the electrical resistance of the blood was not predictably related to the indicator concentration This made it necessary to use an empirical calibration in vitro it has never been ascertained that the in vitro calibration described the in vivo situation

In the present study the average residual ratio of the right ventricle in 14 dogs was 40 4 ± 3 1 per cent which is smaller than that observed by Holt and Allensworth [10] This difference was attributed primarily to the myocardial depressant effect of the barbiturate anesthetic[17 20] used by Holt and Allensworth [10] Secondarily the empirical calibration in vitro in the conductivity method might have raised the residual ratio erroneously [7]

The method presented in the present study offers the following advantages First the dilution curve of ^{131}I MAA from the right ventricle is not obscured by the early appearance of the isotope in the left heart on the radiocardiogram because almost all of the particulates of MAA injected into the right ventricle are trapped in the pulmonary capillaries and do not reach to the left heart [22 23]

Second the difficulties resulting from inadequate mixing of indicator in the right ventricle were minimized by this technique because the total quantity of isotope in the right ventricle is evaluated as a whole by means of the scintillation counter placed on the precordium so as to cover the entire ventricular cavity Third the procedure is technically quite simple making it easily applicable to both clinical and experimental investigations When applied clinically, a more sensitive scintillation detector with a larger crystal (2 inch by 2 inch) should be employed, thereby permitting the injection of a smaller dose of radioisotope

^{133}Xe (80 kev) or ^{85}Kr (510 kev) could be used as the indicator to obtain the right ventricular dilution curve since there would be no interference from radioactivity appearing early in the left heart However, measurement with either of these isotope indicators would not necessarily be superior for just as with ^{131}I MAA the radioactivity transferred to the alveoli would disturb the true exponential downslope of the right ventricular dilution curve

Summary

A method has been presented for determining the right ventricular residual ratio that is the ratio of the end systolic volume to the end diastolic volume during each cardiac cycle ^{131}I MAA was injected as a bolus into the right ventricle and the ratio of isotope remaining in the chamber during the succeeding cardiac cycles was determined with a collimated scintillation counter placed over the right ventricle Since the counter detected the radioactivity from the entire right ventricular cavity potential errors from incomplete mixing were minimized The washout curve from the ventricle was distorted somewhat by the accumulation of isotope in intervening lung tissue This distortion was eliminated by subtracting the build up curve of radioactivity in the lung recorded simultaneously with a second scintillation counter positioned over the lateral chest wall

In 14 dogs anesthetized with chloralose the right ventricular residual ratio was relatively constant at 40 4 ± 3 1 per cent Duplicate measurements differed by less than 3 per cent indicating the good reproducibility of the method.

Right ventricular stroke volume was determined from cardiac output (dye dilution) and heart rate With this and the simultaneously determined residual ratio (^{131}I MAA), end diastolic volume could be calculated Stroke volume and stroke work were highly correlated with end diastolic volume in keeping with the Frank Starling mechanism

The authors express their gratitude to Gail Jamieson Rosann Glas Mary O Sullivan and Richard Trow for their technical assistance to Diann Smith and Eva Toyos for blood gas analysis and Eleanor Register for skillful preparation of the manuscript

Interrelationships between external potassium concentration and lidocaine effects on canine Purkinje fiber

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Recent extensive studies have defined many of the electrophysiologic effects of lidocaine in cardiac tissue[1-9] The major electrophysiologic effects of lidocaine in canine Purkinje fibers at concentrations considered to be in the clinical therapeutic range are to (1) decrease the rate of phase 4 depolarization in the spontaneously beating preparation (2) shorten total action potential duration and effective refractory period and (3) make the refractory period action potential duration ratio greater than one Minimal changes were seen in Purkinje fiber maximum rate of depolarization of phase 0 and in membrane responsiveness Furthermore previous investigators have emphasized utilizing Purkinje fiber preparations that lidocaine has strikingly different electrophysiologic effects as compared to quinidine or procaine amide[2,4-6]

However studies by Singh and Vaughn Williams[10] have offered evidence which refutes the previously described basic differences in electrophysiologic properties between quinidine and lidocaine Although all previous studies[2,4-6] were obtained from tissue perfused by solutions containing 2 7 or 3 0 millimolar potassium Singh and Vaughn Williams experiments were done in solutions with 3 0 and 5 6 millimolar potassium. At an external potassium concentration of 5 6 millimolar the latter authors found that lidocaine reduced the maximum rate of depolarization (dV/dt) of phase 0 at concentrations similar to those found in the blood of successfully treated patients However at an external potassium concentration of 3 0 millimolar high concentrations of lidocaine were necessary to produce the same results

Lidocaine s major role as an antiarrhythmic agent is in the treatment of ventricular tachyarrhythmias it has little or no effect on auricular arrhythmias or in isolated atrial tissue[6,11-15] Substantial data have been accumulated suggesting that alterations in electrophysiologic properties of Purkinje fibers probably are a major causative factor in the development of ventricular arrhythmias[16,17] Therefore it would be ideal to study the electrophysiologic properties of an antiarrhythmic drug utilizing Purkinje fiber preparations Unfortunately in Singh and Vaughn Williams study only rabbit atrial and ventricular muscle was used The purpose of the study was therefore to investigate the effects of alterations in external potassium concentration on the electrophysiologic effects of lidocaine as studied in isolated canine Purkinje fibers

Methods

Mongrel dogs weighing 14 to 22 kilograms were anesthetized with intravenous pentobarbital sodium 30 mg per kilogram Their hearts were rapidly excised and dissected in oxygenated cooled Tyrode s solution Preparations constructed from ventricular septal muscle Purkinje fiber and papillary muscle were dissected from either ventricle and placed in a wax lined tissue bath The bath was perfused with Tyrode s solution gassed with 95 per cent oxygen

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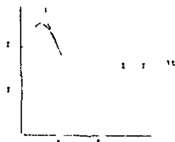
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$$\frac{ESV}{EDV} = \frac{I_{a+1}}{I_a} = \frac{I_{a+2}}{I_{a+1}} = \frac{I_{a+3}}{I_{a+2}} \quad = \frac{I_{n-1}}{I_{n-2}} = \frac{I_n}{I_{n-1}}$$

$$\left(\frac{ESV}{EDV}\right)^{n-a} = \frac{I_n}{I_a}$$

The quantity of indicator in the ventricle decreases exponentially



$$I = I_o e^{-\lambda t}$$

$$\text{then } I_a = I_o e^{-\lambda t_a}$$

$$I_n = I_o e^{-\lambda t_n}$$

$$\left(\frac{ESV}{EDV}\right)^{n-a} = \frac{I_o\, e^{-\lambda t_n}}{I_o e^{-\lambda t_a}} = e^{-\lambda(t_n - t_a)}$$

let N be the number of cardiac cycles $n - a$ which occur in t seconds i e $t_n - t_a$

$$\left(\frac{ESV}{EDV}\right)^{N} = e^{-\lambda t}$$

$$\frac{ESV}{EDV} = e^{-\lambda \frac{t}{N}}$$

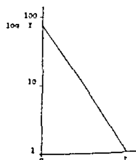
From the electrocardiogram t/N equals the average R R interval

Appendix B

The exponential gradient λ is calculated using regular logarithms as follows from a general equation of

$$I = I_o\, e^{-\lambda t}$$

$$\begin{aligned} \text{Log } I &= \log I_o \; e^{-\lambda t} \\ &= \log I_o + \log e^{-\lambda t} \\ &= \log I_o - \lambda t \;\; \log e \\ &= \log I_o - \lambda t \;\; 0.4343 \\ &= -0.4343\lambda t + \log I_o \end{aligned}$$



$$\frac{\text{Log } I}{t} = -0.4343\lambda + \frac{\text{Log } I_o}{t}$$

$$\text{therefore,} \quad -\lambda = \frac{\log I - \log I_o}{0.4343\, t}$$

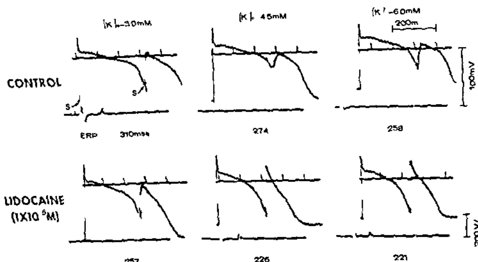


Fig 2 The effect of changes in $[K^+]_o$ and lidocaine perfusion on refractory period measurements in canine Purkinje fiber The upper portion of the figure shows refractory period measurements obtained in one cell at various $[K^+]_o$ The effective refractory period (ERP) value in milliseconds is shown below each panel S_1 and S_2 identify the basic and premature stimulus respectively A time and voltage calibration is shown in the upper right of the figure The bottom of the figure shows similar measurements obtained in the same cell following lidocaine 1×10^{-5}M *perfusion*

ness All measurements were obtained at a stimulation cycle length of 800 msec (75 per minute) Recordings were obtained in the control state at one external potassium concentration (3 0 4 5 or 6 0 millimolar) and subsequently following 30 minutes of superfusion with 1×10^{-5} M lidocaine and a similar external potassium concentration Statistical comparisons were made utilizing the student s t test for paired samples Data were expressed as mean values ±S E M

Results

Effect of altering external potassium concentration alone on action potential characteristics As shown in Table I progressive decrease in Purkinje fiber dV/dt resting potential and total amplitude was noted following exposure to increasing concentrations of external potassium Higher concentrations of external potassium also shortened both the effective refractory period and the action potential duration at 50 per cent and 75 per cent of full recovery (Figs. 1 and 2) With few exceptions all parameters show statistically significant differences when comparisons were made between values obtained at various external potassium concentrations (Table II)

Effect of external potassium concentration lidocaine on action potential characteristics To differentiate clearly the effects of lidocaine relative to changes in external potassium concentration data obtained with and without lidocaine perfusion at each external potassium concentration were tabulated and compared statistically (Table I) Furthermore the effect of lidocaine was compared at each $[K^+]_o$ (Table IIIA and B) The dV/dt increased after lidocaine at an external potassium concentration of three millimolar whereas a decrease was observed after lidocaine perfusion at an external potassium concentration of 6 0 millimolar At an external potassium concentration of 4 5 millimolar no significant change in dV/dt was noted following lidocaine The effects on overshoot and total action poten

Table II Statistical evaluation of the effect of changes in $[K^+]_o$ on action potential characteristics of canine Purkinje fibers

	K3 vs K4 5	*K3 vs K6*	*K4 5 vs K6*
dV/dt	NS	†	†
Resting potential	†	†	†
Overshoot	†	†	NS
Tamp	NS	†	†
ERP	†	†	†
50 per cent APD	†	†	†
75 per cent APD	†	†	†

NS = Not significant.
† = $p < 0.01$

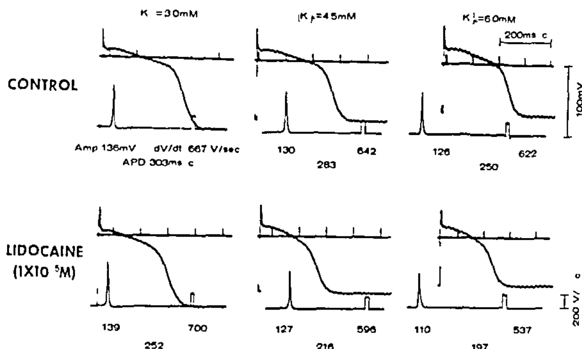


Fig 1 The effect of changes in [K+]o and lidocaine perfusion on action potential characteristics in canine Purkinje fiber The upper portion of the figure illustrates typical action potentials from one cell at [K]o of 3 0 4 5 and 6 0 mM Total amplitude in millivolts phase 0 dV/dt in volts per second and action potential duration at 75 per cent of recovery in milliseconds are shown below each panel A time and voltage calibration are shown at the upper right of the figure A 200 V per second calibration for dV/dt is shown to the bottom right of the figure The lower portion of the figure shows the same cell following perfusion with lidocaine 1 × 10 5M Similar action potential characteristics are shown below the panels

Table I Effect of K+ lidocaine on canine Purkinje fiber

	K+ = 3 0 mM	+LIDO	K+ = 4 5 mM	+LIDO	K+ = 6 0 mM	+LIDO
	553 ±	570 ±	531 ±	533 ±	480 ±	442 ±
dV/dt	41 4	30 1	19 5	18 6	9 6	13 7
Resting potential	96 ±	97 ±	88 ±	87 ±	78 ±	78 ±
	1 2	1 3	1 3	1 5	2 2	2 4
	33 ±	34 ±	39 ±	39 ±	38 ±	37 ±
Overshoot	2 7	0 9	2 3	2 5	2 3	0 1
Total amplitude	130 ±	131 ±	127 ±	127 ±	117 ±	113 ±
	2 9	1 6	2 6	2 4	2 4	3 1
	314 ± †	277 ±	295 ± †	258 ±	275 ±	242 ± *
ERP	5 9	9 5	8 3	10 5	8 5	9 4
50 per cent of APD	274 ± †	223 ±	234 ± †	194 ±	218 ±	169 ±
	7 4	8 4	5 5	4 0	7 5	3 5
75 per cent of APD	312 ± †	273 ±	280 ± †	238 ±	266 ±	221 ±
	8 9	11 6	5 0	5 6	6 3	9 2

M ± S E M
N = 7
* = P<0 05
† = P<0 01

and 5 per cent CO_2 at a constant rate of 8 c c per minute The temperature in the bath was con stantly maintained at 37 ± 0 5° C The pH of the final Tyrode solution was 7 40 ± 0 03 (mean ± S E M) The composition of the Tyrode solution in millimoles per liter, was NaCl 137 $NaHCO_3$ 25 dextrose 5 5 NaH_2PO_4 1 8 CaCl 2 7 $MgCl_2$ 0 5 and KC1 3 0 4 5 or 6 0 The techniques used for stimulation and recording have been described previously [4] The following parameters were measured (1) resting potential (2) overshoot (3) total action potential amplitude (4) maximum rate of rise of phase 0 (dV/dt) (5) effective refractory period (6) action potential duration at 50 per cent and 75 per cent of full recovery period and (7) membrane responsive

bly alter the electrophysiologic properties of an anti arrhythmic agent such as lidocaine Our initial results have shown that slight alterations in external potassium concentration alone can influence the maximum rate of rise of phase 0 (dV/dt) resting potential effective refractory period, and action potential duration (Table I) These results in general correspond to those previously reported by Vassalle[24] in sheep and calf Purkinje fiber at potassium concentrations of 2 7 and 5 4 millimolar No significant effects on membrane responsiveness relative to changes in external potassium concentration were discernible following perfusion with 3 0 or 4 5 millimolar potassium However depression of peak V_m was observed following 6 0 millimolar potassium presumably reflecting lowering of the resting potential and, therefore some inactivation of the sodium carrier system Furthermore both lidocaine perfusion and an increase in $[K^+]_o$ produce an increase in gK Therefore the combination effect of a $[K^+]_o$ of 6 0 and alterations in cable properties by lidocaine could produce the observed decrease in dV/dt independent of alterations in sodium kinetics

Effect of changes in external potassium concentration associated with lidocaine perfusion In 3 0 and 4 5 millimolar potassium Tyrode s perfusion with lidocaine did not statistically alter action potential amplitude resting potential or dV/dt These findings correspond to results previously reported[24] However in 6 0 millimolar potassium Tyrode s lidocaine produced significant depression in phase O dV/dt Little change was noted in the control membrane responsiveness curves obtained in Tyrode s with 3 0 or 4 5 millimolar potassium. However 6 0 mM potassium significantly depressed V_m Subsequent lidocaine administration in 6 0 mM potassium Tyrode s resulted in more prominent depression of V_{max} The mechanism of further depression of $\dot{V}_m$ and dV/dt following lidocaine perfusion at $[K^+]$ = 6 is unexplained by our present data but may be related to lidocaine s effects on passive cable properties i e a decrease in R_M and a decrease in R_S leading to a decrease in dV/dt and V_{max} which would be apparent only at the lower V_M seen at $[K^+]_o$ = 6 0 This finding is in fact opposite to those previously reported at lower potassium concentration with lidocaine and consistent with some of the observations of Singh and Vaughn Williams[10] However the decrease in resting potential, amplitude and dV/dt seen as a result of high potassium Tyrode s would in itself be anticipated to diminish conduction velocity[26,27]

Nevertheless lidocaine produced significant shortening of both effective refractory period and action potential duration at all external potassium concentrations tested More specifically the effective refractory period action potential duration ratio was always greater than one following lidocaine administration in any of the external potassium concentrations This effective refractory period action potential duration relationship has been considered to be one of the major mechanisms of antiarrhythmic drug effect.[25] Therefore although potassium concentrations in the higher physiologic range may somewhat alter the electrophysiologic properties of lidocaine many of the previous electrophysiologic properties considered as vital in terms of the drug s antiarrhythmic actions persist It appears likely that at high external potassium concentrations the alterations in lidocaine s electrophysiologic effects such as changes in the phase 0 dV/dt and membrane responsiveness are less likely to prove to be the mechanism of action of this antiarrhythmic drug in ventricular specialized conducting tissue

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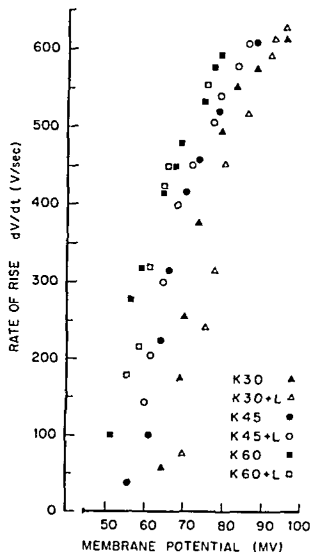


Fig 3 The effect of [K⁺]o lidocaine on membrane responsiveness in canine Purkinje fiber Membrane potential in millivolts is plotted on the horizontal axis and phase 0 dV/dt in volts per second is plotted on the vertical axis A legend is seen to the right of the figure

tial amplitude paralleled the results seen with *the rate of rise of phase 0 In contrast lidocaine* exerted no significant effect on resting potential regardless of the external potassium concentration Also alterations in external potassium concentration did not significantly affect lidocaine s induced changes in effective refractory period or action potential duration at 50 per cent of full recovery However when action potential duration was measured at 75 per cent of full recovery more prominent changes were noted following lidocaine in 6 0 millimolar potassium Tyrode s (Table IIIA)

Effect of external potassium concentration lidocaine on membrane responsiveness Determinations of membrane responsiveness were

Table IIIA Lidocaine's electrophysiologic effect in canine Purkinje fiber percentage change at each [K+]o

	K3	*K4 5*	*K6*
dV/dt	3 1 ± 3 2	0 3 ± 0 9	-8 0 ± [illegible]2
Resting potential	-0 6 ± 1 2	0 1 ± 5 2	0 6 ± 0 9
Overshoot	2 7 ± 3 3	-1 1 ± 1 7	-4 7 ± 3 3
Tamp	1 5 ± 1 4	-0 6 ± 0 7	-2 9 ± 2 5
FRP	-11 9 ± 2 4	-12 8 ± 2 5	-12 1 ± 2 3
50 per cent APD	-18 6 ± 2 9	-18 1 ± 1 6	-2[illegible] 3 ± 3 1
75 per cent APD	-12 7 ± 1 8	-15 3 ± 1 5	-17 4 ± 3 3

Table IIIB Statistical evaluation of the difference in lidocaine s electrophysiologic effects in canine Purkinje fibers at various [K+]o

	K3 K4 5	*K3 K6*	*K4 5 K6*
dV/dt	†	‡	‡
Resting potential	NS	NS	NS
Overshoot	†	‡	†
Tamp	‡	‡	†
FRP	NS	NS	NS
50 per cent APD	NS	NS	NS
75 per cent APD	†	‡	†

N = 7
NS = not significant.
† = $p < 0.05$
‡ = $p < 0.01$

obtained in five experiments and a typical example is shown in Fig 3 No significant difference was noted between curves obtained in 3 0 or 4 5 millimolar potassium Tyrode's However following perfusion with 6 0 millimolar potassium peak V_{max} was depressed

Addition of lidocaine produced no significant changes in the membrane responsiveness curve at external potassium concentrations of 3 0 or 4 5 millimolar However at 6 0 millimolar potassium lidocaine further depressed peak V_{max}

Discussion

Effect of changes in external potassium concentration Although electrophysiologic effects of alterations in external potassium concentration on *cardiac tissues including Purkinje fibers*, from various species have been described most of these studies were carried out using pronounced variations in potassium concentration [18-24] However the purpose of the present study was to see if alterations of external potassium concentration within a relatively narrow range could possi

Case reports

Sustained accelerated idioventricular rhythm

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Recent studies have elucidated the clinical picture of patients with accelerated idioventricular rhythm[1] This arrhythmia almost always occurs within 48 hours of an acute myocardial infarction is intermittent and is generally benign[2-5] Reported herein is an unusual case of sustained accelerated idioventricular rhythm documented by His bundle electrocardiographic studies that appeared six weeks after myocardial infarction and was successfully treated by a suppressant anti arrhythmic drug

Case report

A 73 year-old man was admitted to the coronary-care unit at San Francisco General Hospital on Jan 19 1973 with a history of severe pressing precordial pain Physical examination revealed no abnormalities except for a pulse rate of 120 beats per minute and a loud presystolic gallop The systemic blood pressure was 130/80 mm Hg Serial electrocardiograms (ECG) were characteristic of an acute inferior myocardial infarction (Fig 1 A) His course was complicated by the de elopment of multiple pr mature ventricular contractions transient left bundle branch block and evidence of left entricular decompensation The patient was treated with diuretics and digoxin and kept on an oral daily maintenance dose of 0 25 mg of digoxin At discharge (Feb 9 1973) the s gns and symptoms of heart failure were no longer present and the systemic pre ure was 120 to 130/80 to 85 mm Hg the ECG showed sinus rhythm with evolving inferior myocardial infarction (Fig 1 B) The patient returned to the outpatient clinic on Mar 2 1973 complaining of easy fatigability during the la t three days The pulse rate was 100 beats per minute and regular and the blood pressure was 100/70 mm Hg The remaind r of the physical examination was unremarkable The ECG was initially interpreted as showing a junctional rhythm with right bundle branch block at the rate of 100 beats per minute (Fig 2) Serum electrolytes were within normal limits and the digoxin level was 0 5 ng per milliliter Digoxin was discontinued but the symptoms and arrhythmia persisted he was readmitted to the coronary care unit on Mar 6 1973 Twenty four hours of continuous ECG monitoring documented persistence of the arrhythmia and a His bundle electrogram was performed to clarify the nature of the cardiac rhythm disturbance

Methods and procedure

A His bundle recording was obtained according to the technique of Scherlag and associates[6] In brief a hexapolar electrode catheter was inserted percutaneously into the right femoral vein and positioned across the tricuspid valve The catheter was connected to a junction box that was in turn connected to an Electronics for Medicine DR 12 recorder with filter settings at 40 to 500 c p s The His bundle electrogram and X Y and Z leads of the Frank system were displayed and recorded simultaneously His bundle recordings were obtained from the distal electrode pair while intra atrial recordings were obtained from a more proximal electrode pair

Results

The surface electrogram showed a wide ventricular complex with a right bundle branch configuration that was not preceded by a His deflection in the His bundle electrogram (Fig 3 A) No atrial activity was discernible from the surface or intra atrial leads Treatment was initiated with intravenous infusion of procaine amide at a rate of 20 mg per minute with the electrode catheter in place After infusion of 300 mg of procaine amide rare capture beats appeared (Fig 3 B) The rhythm disorder continued to stabilize and reverted to sinus rhythm without ectopic activity after infusion of 1 Gm of procaine amide (Fig 3 C) With return to sinus

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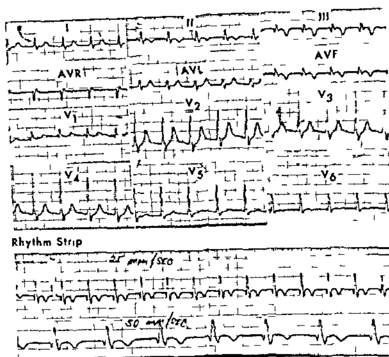


Fig 2 ECG during first outpatient clinic visit on Mar 2 1973 showing tachycardia with right bundle branch block pattern.

and because the active ventricular focus was still present six days after the drug was discontinued.

In previous electrophysiologic studies of patients with accelerated idioventricular rhythm the ectopic origin of the acute focus was localized to either the proximal segments of the fascicles of the conduction system[12] or to more distal sites[13] in the conduction system In the present report the presence of a ventricular focus was substantiated by the absence of His deflection preceding the ventricular complex and by definite fusion beats that appeared after initiation of intravenous procaine amide therapy The absence of atrial activity was due to either sinoatrial arrest isoarrhythmic atrioventricular dissociation or more likely to retrograde ventriculoatrial capture with P wave buried within the QRS complex The latter hypothesis best explains the sustained nature of this arrhythmia in this patient Sinoatrial arrest and atrioventricular dissociation are unlikely causes since suppression of the active ventricular focus by procaine amide allowed for gradual emergence of sinus rhythm at a rate of 80 beats per minute

Therapy of this rhythm disorder remains controversial Some investigators believe that no active therapy is required in view of the transient usually benign nature of this dysrhythmia[1,5] Others[14,16] suggest the use of atropine or atrial pacing to overdrive suppress the active ventricular focus Likewise differing recommendations regarding use of lidocaine[14] and/or procaine amide have been set forth Some investigators believe largely on theoretical grounds that these agents are in fact contraindicated in the treatment of accelerated idioventricular rhythm[15,16] In the present case choice of appropriate treatment posed important therapeutic problems Because the idioventricular rate was 100 beats per minute we were reluctant to employ atropine or atrial pacing as the higher atrial rate required for arrhythmia control to suppress the arrhythmia might indeed prove hazardous in this patient with recent myocardial infarction[17] On the other hand absence of atrial activity in either surface or intra atrial electrograms introduced the possibility of sinus arrest with the possibility that the idioventricular focus was the only reliable cardiac pacemaker If the latter possibility were true then suppressant therapy could by abolishing this pacemaker result in either cardiac asystole or severe sinus bradycardia Because of the patient s decrea ed

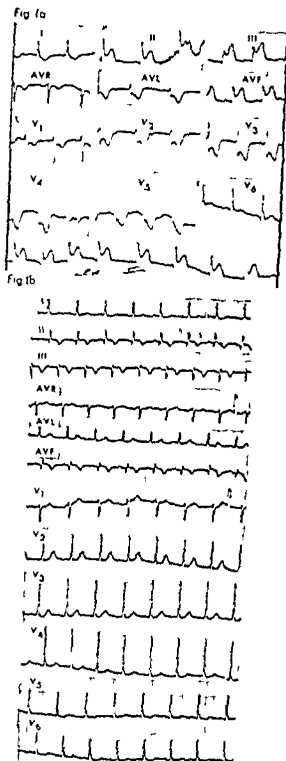


Fig 1 *A* Admission ECG on Jan 19 1973 showing acute inferior wall myocardial infarction *B* Discharge ECG on Feb 9 1973 showing sinus rhythm and evolving inferior wall myocardial infarction

rhythm blood pressure rose to 130/80 mm Hg The catheter was removed and quinidine sulfate (300 mg) was administered orally every six hours Over the ensuing 48 hours transient bouts of accelerated idioventricular rhythm (Fig 4) appeared until a therapeutic level (3 1 mg per liter) of quinidine was attained Serial ECG s while in sinus rhythm revealed no new changes and serial creatine phosphokinase glutamine oxaloacetic transaminase and lactic dehydrogenase levels were within the normal range The patient was discharged on Mar 16, 1973 and two weeks later quinidine was discontinued and 10 hour ECG monitoring (Avionics Electrocardiorecorder Model 400) revealed rare premature ventricular beats Three weeks after discharge he had no symptoms of palpitation dyspnea or easy fatigability The ECG showed sinus rhythm at a rate of 80 beats per minute and was unchanged compared with previous tracings

Discussion

Accelerated idioventricular rhythm most commonly occurs within 48 hours after acute myocardial infarction or more rarely is associated with digitalis intoxication[8,9] For example Rothfield and colleagues[3] found this rhythm disturbance in 30 of 100 patients with acute myocardial infarction observed under continuous monitoring Moreover, Grace and Yarvote[10] found no evidence of accelerated idioventricular rhythm in 117 patients with acute myocardial infarction who were monitored for seven to 12 days in an intermediate coronary care unit Similarly[11] analyses of six hour ECG rhythm strips in 100 patients studied three weeks after probable or definite acute myocardial infarction failed to reveal any instances of accelerated idioventricular rhythms Massumi and Ali[9] on the other hand reported this arrhythmia in 30 patients with a variety of cardiac diseases including several patients with prior history of acute myocardial infarction It is not clear, however from their studies whether or not acute ischemic episodes were excluded in this group of patients In all reported cases however the arrhythmia was intermittent and generally benign Therefore the present report is unique in several respects The arrhythmia was noted six weeks after myocardial infarction and was accompanied by a lowering of blood pressure and symptoms of easy fatigability It was probably present (as gauged by symptoms) for several days and was documented to be sustained during 24 hours of continous ECG monitoring Moreover, in the present report an acute ischemic process was excluded by the absence of any cardiographic changes or serum enzyme rise Digitalis toxicity is an unlikely cause of this arrhythmia because the initial level was in the low therapeutic range

pressure to normal levels The unique aspects of this case and therapeutic considerations in the management of this problem are discussed

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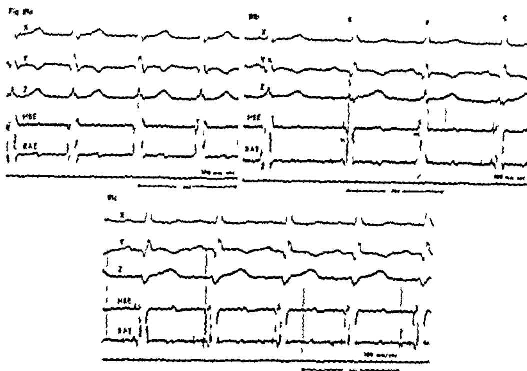


Fig 3 *A* Control His bundle electrogram His deflection does not precede QRS complexes. *HBE* = His bundle electrogram *RAE* = right atrial electrogram *B* After a 300 mg intravenous infusion of procaine amide there is suppression of the ventricular focus, allowing for emergence of capture (*C*) and fusion (*F*) beats which are preceded by His deflections (*H*) *A* = atrial electrogram *C* His bundle electrogram after 1 Gm of procaine amide infusion showing complete restoration of sinus rhythm

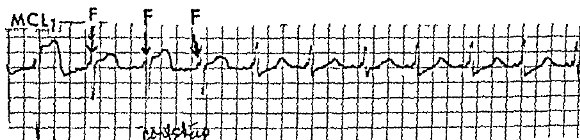


Fig 4 MCL_1[7] strip on Mar 6 1972 showing intermittent accelerated idioventricular rhythm The first beat is normally conducted and is followed by a succession of three fusion beats (*F*) and finally resurgence of the active ventricular focus

blood pressure and symptoms it was decided to initiate therapy with procaine amide with an intracardiac pacemaker in place and with a standby generator ready for intracardiac pacing The disappearance of symptoms and the normal systemic pressure after return of sinus rhythm suggested that these findings were related to increased heart rate and/or loss of proper atrioventricular synchronization

In summary a unique case of sustained, accelerated idioventricular rhythm first appearing approximately six weeks after myocardial infarction is reported The focus of the arrhythmia was localized below the atrioventricular node by His bundle ECG studies A successful treatment regimen for this disorder included use of intravenous procaine amide with standby intracardiac pacemaker

Summary

A 73 year old white man became easily fatigued and hypotensive six weeks after a documented acute inferior myocardial infarction Continuous ECG monitoring showed a sustained tachycardia with a right bundle branch block pattern A His bundle electrogram showed no His deflection prior to ventricular activation The patient was successfully treated with intravenous procaine amide resulting in reversion to sinus rhythm loss of symptoms and return of blood



Fig 1 Patent coronary artery with normal intima muscular and adventitial layers (Hematoxylin and eosin × 80)

and diuretics while the blood losses were replaced with packed cells There appeared to be no clinical improvement The patient became severely acidotic and was treated with intravenous bicarbonate and isoproterenol to increase cardiac output. Only transient improvement occurred No significant urine output could be achieved by any of the above and at 57 hours of age continued metabolic acidosis and elevation of serum potassium heralded renal failure Treatment with bicarbonate continued and sodium polystyrene sulfonate (Kayexalate) enemas were given At 93 hours of age the patient had a prolonged episode of bradycardia and cardiac arrest Cardiac resuscitation was unsuccessful

At autopsy the heart weighed 20 grams Grossly there were darkened areas over the posterior wall of the left ventricle and anterior right ventricle There were no vascular abnormalities noted other than the patent ductus arteriosus The wall of the left ventricle was soft and had gross subendocardial hemorrhage in the wall of the septum the free wall of the left ventricle and the anteroinferior wall of the right ventricle Coronary arteries appeared normal and were patent There were four major branches originating from the aorta innominate left carotid left subclavian and left vertebral artery The kidneys were congested and the medullae hemorrhagic as contrasted to the pale cortices The renal arteries were patent The ureters and bladder were normal Grossly the brain and meninges were unremarkable

Microscopically the heart showed transmural infarction of the left ventricle and anteroinferior area of the right ventricle extensive in degree The coronary arteries were normal The lungs had areas of accumulation of foamy histiocytes in alveoli together with degenerating and necrotic squamous cells. Many capillaries were congested and alveoli not aerated. Sections of the kidney revealed extensive necrosis into the proximal and distal tubules and necrosis of many of the collecting duct cells. The glomeruli and renal vessels were unremarkable Brain sections had normal architecture In the cerebellum the Purkinje s cells were swollen with focally absent nuclei There was no evidence of disseminated intravascular coagulation

Discussion

The autopsy findings of extensive myocardial infarction in our patient came as a distinct surprise It was immediately apparent however that such a diagnosis readily explained the clinical state of cardiogenic shock with hypotension oliguria and renal failure as well as the congestive heart failure manifested by cardiomegaly and pulmonary vascular congestion Similarly the cardiac catheterization findings of extreme left ventricular dysfunction were consistent with this diagnosis and the ECG which was thought to represent WPW syndrome may in truth have been a matter of myocardial infarction The absence of any occlusive coronary artery disease or anomaly is most unusual and difficult to explain particularly in the absence of any demonstrable form of congenital heart disease Areas of myocardial infarction have been noted in neonates who died from congenital heart disease with such lesions as pulmonary valvular stenosis aortic valvular stenosis transposition of the great vessels and total anomalous pulmonary venous return [1] In such cases however the areas of infarction have not generally been associated with clinical deterioration or related to the cause of death Franciosi and Blanc[2] studied 44 such

Myocardial infarction in the newborn. A case report complicated by cardiogenic shock and associated with normal coronary arteries

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Myocardial infarction due to coronary artery occlusion in the neonatal period has been reported several times.[1] Furthermore, it is not uncommon to find histologic evidence of myocardial necrosis in neonates who have died of congenital heart disease, even in the absence of gross coronary pathology or anomaly.[2-6] The finding of myocardial infarction in the neonate with normal coronary arteries and not associated with congenital heart disease is extremely rare, however, which prompted us to report this case.[2]

Case report

A white female infant, 2,962 gram product of a 21 year old gravida 1, para 0, was delivered at 40 weeks' gestation following an uncomplicated prenatal course. Because of hypotonic uterine contractions, Pitocin augmentation was used five hours prior to delivery, at which time the heart rate increased from 160 to 200 beats per minute. It returned to normal 30 minutes prior to delivery. Three and a half hours prior to delivery the mother's temperature was 100.4° F., but urine and lochia cultures were negative. Meconium staining of the amniotic fluid was noted one hour prior to delivery. Delivery was without difficulty under saddle anesthesia with the use of a vacuum extractor. Labor lasted 11 ½ hours. Placental examination was normal.

Examination of the neonate revealed an extremely flaccid infant with no spontaneous movements other than ocular and eyelid. Apgar score at 1 minute was 6 and at 5 minutes was 8. The hands and feet were cyanotic, the extremities moderately dusky, and the trunk and head a dusky pink. There was a caput succedaneum extending over the left parietal and occipital bones and a small left scleral hemorrhage. The suck was poor, no cry was elicited, and the respiratory rate was 50 breaths per minute. The heart rate was 186 beats per minute with single extrasystoles every five to 10 beats and occasional runs of tachycardia. Pulses were extremely weak in all extremities and flush blood pressures of 52 mm. Hg in the right arm and 40 mm. Hg in all other extremities were obtained. Moro and deep tendon reflexes could not be elicited and pinprick examination revealed a negligible response. At one half hour of age arteriolar capillary heel stick blood gases were pH 7.12, Po_2 53, CO_2 26.9 mEq. per liter, O_2 saturation 75 per cent, hematocrit 48 per cent. Electrocardiogram (ECG) at 45 minutes of age demonstrated a heart rate of 186 with no arrhythmias and a QRS interpreted as a type A WPW (Wolff-Parkinson-White) syndrome. The patient was placed in 40 per cent oxygen and umbilical artery catheter inserted. The acidosis was corrected with sodium bicarbonate over a 60 minute period. A lumbar puncture was obtained with red blood cell count of 248,000, 44 polymorphonuclear leukocytes and 20 lymphocytes. This was thought to be traumatic. The child was begun on ampicillin and kanamycin. At 90 minutes of age the skin color improved, the extremity movement was fair, and arterial blood gases were pH 7.45, Po_2 72.

During the first 36 hours of age the child did not urinate and catheterization yielded 3 c.c. of urine which was heavy with sediment. Chest x-ray demonstrated cardiomegaly with left lung hypoperfusion. The liver edge was 1 cm. below the right costal margin. At 42 hours of age a four chamber cardiac catheterization via the umbilical vein and artery was performed. Angiocardiograms were interpreted as showing the pulmonary artery arising anteriorly from the right ventricle and feeding the aorta via a patent ductus arteriosus. The left ventricular injection showed extremely poor ventricular contraction with opacification of a normal appearing aorta. The left ventricular pressure was 48 with left ventricular end diastolic pressure (LVEDP) of 17. Right ventricular pressure recorded simultaneously was 60 with RVEDP of 12. Aortic pressure was 48/38. The LVEDP was distinctly elevated with profound systemic hypotension. The right and left atrial mean pressures were elevated. Arterial saturation was 80 per cent and no right heart chamber oxygen stepup was noted. The patient was treated with digoxin

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raised was that of forceful uterine contractions secondary to oxytocin causing increased pressure load on the head thereby increasing the intracranial pressure leading to coronary vasoconstriction This again seems unlikely It would seem possible that the explanation for diffuse myocardial *necrosis* which clinically seems to have been present at birth and accounted for a picture of cardiogenic shock may have had its inception during the period of fetal distress shortly before delivery During this period of time the increased fetal heart rate with its concomitant increased oxygen demand may well have been associated with a period of fetal hypoxia leading to diffuse intramyocardial necrosis After birth isoproterenol treatment may have extended the size of the infarction but was given only a short clinical trial

Rowe and Hoffman[7] described three mature *newborn infants with a syndrome of cyanosis* congestive failure and acute left ventricular failure These patients also mimicked severe congenital heart disease with weak arterial pulses and liver enlargement, and suggested the diagnosis of hypoplasia of the left heart Rowe and Hoffman postulated that there was impaired coronary perfusion to the right and left ventricles because of increased work demands created by unusually brisk pulmonary vasoconstriction from hypoxia All of their patients went on to recover A reasonable assumption is that our case represents a further progression of the above clinical state to myocardial infarction

Coronary thrombosis is certainly not a prerequisite for myocardial *infarction* [8] Roberts[9] noted that thrombi are present at autopsy in only 10 per cent of adults who die suddenly or in whom myocardial necrosis is limited to the left ventricular subendocardium and in about 50 per cent of patients with transmural myocardial infarctions Demonstrable coronary artery thrombi are considerably more common in *patients who have* survived myocardial infarction for longer periods of time and are not infrequently present in those exhibiting a terminal picture of shock or congestive failure These findings have suggested the concept that coronary artery thrombosis is the consequence rather than the cause of myocardial infarction

Although the *etiology of* this patient s diffuse myocardial necrosis remains a matter of speculation *it is of considerable* interest to note that it did indeed occur and presented a clinical picture suggesting hypoplastic left heart syndrome It is hoped that by reason of this report the possibility of myocardial infarction will be entertained in the differential diagnosis of cardiogenic shock in the neonatal period

Summary

Fatal myocardial infarction occurring in a neonate is reported The patient presented with a clinical picture of cardiogenic shock simulating a hypoplastic left heart syndrome Etiology of the *myocardial infarction is uncertain for the coronary* arteries were patent anatomically and histologically normal and there was no significant associated cardiac defect The possible etiologies in relationship to myocardial infarction in the neonatal period are presented

The authors wish to express their appreciation for the support rendered by the Department of Medical Research and Development personnel in completion of this paper

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Fig 2 Junctional zone showing necrotic muscle with polymorphonuclear infiltration on right. Toward the left is more normal appearing muscle with two patent coronary arteries. (Hematoxylin and eosin × 20)

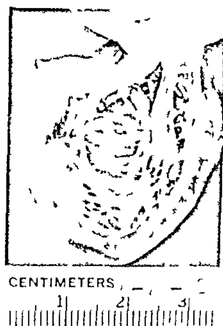


Fig 3 Gross specimen of the cut surface of the left ventricle showing extensive myocardial infarction

hearts at autopsy and found infarction in 33 These infarcts were localized to papillary muscles and subendocardial ventricular myocardium and none were associated with occlusive vascular disease The frequency of infarcts was highest in aortic stenosis (100 per cent) pulmonary stenosis (89 per cent) total anomalous pulmonary venous drainage (80 per cent) and transposition of the great vessels (39 per cent) It is felt that most of these infarcts were related to work hypertrophy of the involved ventricle with relative ischemia and eventual infarction With hypoplasia of the ventricle as in aortic valve or pulmonary valve atresia myocardial scarring may be related to endocardial fibroelastosis and decreased perfusion and oxygenation

Gault and Usher[4] state that a primary intimal lesion associated with coronary artery thrombosis and death in neonates is extremely unusual but that mild intimal thickening is a frequent finding Moon[5] cites evidence which suggests a relationship between these areas of focal infantile thickening and coronary artery disease in later life The focal localization is maximal in the proximal part of the epicardial branches of the coronary arteries particularly the left anterior descending with male predominance

Our case without associated congenital defects or coronary vascular disease most closely parallels the case of Ravich and Rosenblatt[3] who reported a case of myocardial infarction in a neonate who at autopsy had normal coronary arteries In both instances the mother received Pitocin just before delivery The pathogenesis was obscure but raised several possibilities including the pressor and oxytonic fractions of posterior pituitary gland extracts The pressor substances may cause a vasoconstriction of the coronary arteries This possibility seems remote however since in many patients labor is induced with oxytocin without reportable incidence of myocardial infarction The second possibility

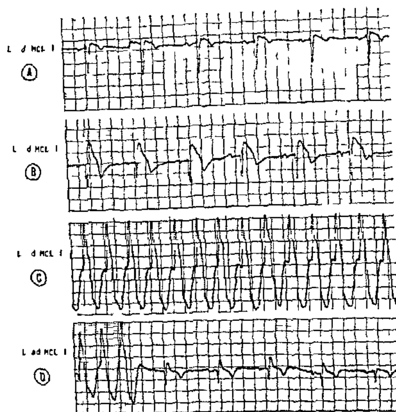


Fig 1 Patient 1 A MCL I monitor lead tracing demonstrates typical changes that occurred during episodes of chest pain (A) normal pattern, (B) ST segment elevation (C) short run of ventricular tachy ardia and (D) reversion to normal rhythm

tent (Fig 3) There were no dyskinetic areas of the left ventricle The postoperative resting ECG was normal (Fig 4A) An exercise ECG revealed no ST segment changes at a heart rate of 140 beats per minute but was discontinued because the patient complained of leg pain (Fig 4B)

Case 2 A 51 year old white man was admitted to the hospital because of recurrent chest pain described as a pressure sensation in the lower substernal region Initially the pain occurred in the morning after awakening from sleep but then nocturnal pain developed There were no episodes of chest pain associated with exertion The pain had been present for about one month prior to admission to the hospital The patient denied dyspnea or syncopal episodes There was no family history of coronary artery disease but the patient's father had diabetes mellitus The physical findings and laboratory data were normal.

During the hospital course frequent episodes of chest pain associated with ST segment elevation were noted A 12 lead ECG revealed these changes to be in Leads II III and aVF (Fig 5A) With chest pain, ST segment elevation, and QRS changes, there were often PVC s and short runs of ventricular tachycardia (Fig 5B)

These episodes persisted over a 25 day period of continuous monitoring in the CCU despite medical therapy consisting of Pronestyl (250 mg every four hours) propranolol (80 mg daily) Isordil (to tolerance) and an infusion of lidocaine at 4

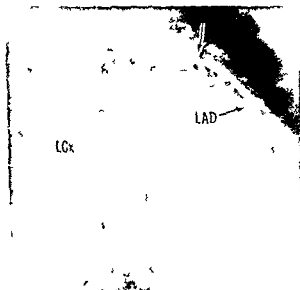


Fig 2 Patient 1 A right anterior oblique view (60 degrees) of the left coronary artery demonstrates high grade obstruction in the left anterior descending (LAD arrows) and diffuse disease in the left circumflex coronary artery (LCX)

Coronary artery surgery for recurrent ventricular arrhythmias in patients with variant angina

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Serious ventricular arrhythmias in patients with variant angina due to occlusive coronary artery disease may be difficult to control with conventional medical therapy In patients with such arrhythmias coronary artery bypass surgery may be indicated as treatment even though chest pain is not severe The following cases illustrate successful surgical therapy of recurrent ventricular arrhythmias in two patients with Prinzmetal s variant angina Medical therapy failed to adequately control the tachyarrhythmia Coronary arteriography demonstrated severe occlusive vascular disease and following coronary artery surgery the arrhythmias were abolished

Case reports

Case 1 A 41 year old white man was admitted to the hospital complaining of left chest pain of two months duration The pain was described as a pressure sensation radiating to the jaw and left arm and was not related to exercise food intake or emotion On several occasions the pain awakened the patient during the night The patient smoked two packages of cigarettes daily despite the presence of bronchial asthma for the previous 17 years Adult onset diabetes mellitus had been treated with diet and tolbutamide for five years One parent suffered a myocardial infarction and both parents had chronic obstructive lung disease

Occasional inspiratory wheezes were detected in both lungs The heart was of normal size and a fourth heart sound was present No cardiac murmur was detected

The serum triglycerides were 540 mg per 100 ml the blood cholesterol was 245 mg per 100 ml and the glucose tolerance test was abnormal

Early in the hospital course three syncopal episodes associated with chest pain occurred but were not monitored by an ECG Thereafter frequent episodes of chest pain followed by ST elevation QRS widening and short runs of ventricular tachycardia occurred (Fig 1) ST segment elevation was confined to anterior precordial leads Six of these episodes resulted in ventricular tachycardia and/or ventricular fibrillation which were successfully treated by D C shock in four instances and by a bolus of lidocaine in two instances. The patient was treated intensively in the coronary care unit (CCU) for 55 days Quinidine (200 mg every four hours) Pronestyl (750 mg every three hours) propranolol (120 mg daily) Isordil (to tolerance) atropine and lidocaine (4 to 5 mg per minute) either alone or in combination, failed to suppress the ventricular arrhythmias An attempt at suppressing the arrhythmia by increasing the ventricular rate by pacing was unsuccessful

Coronary arteriography demonstrated high grade obstruction in the left anterior descending coronary artery (LAD) and diffuse disease in the circumflex branch of the left coronary artery (LCX) (Fig 2) Diffuse disease was also present in the right coronary artery (RCA) While waiting for operation the patient had another episode of chest pain and syncope

Shortly after induction of anesthesia the patient developed hypotension which did not respond adequately to pressor agents The chest was opened and cardiac massage was initiated A 1 5 mm probe could not be passed through the lesion in the LAD and in spite of a mean aortic pressure of 60 mm Hg there was no antegrade flow through the LAD indicating a highly obstructive lesion Two aorticocoronary saphenous vein bypass grafts (ACSVG) from the ascending aorta were anastomosed one each to the LAD and to the posterior descending coronary artery (PDA) The flow rate to the LAD was 90 ml per minute and the flow rate to the PDA was 65 ml per minute as measured by an electromagnetic flowmeter at the time of operation

The patient had an uneventful postoperative course Since operation he has had no chest pain syncopal episodes or suspected or documented arrhythmias Coronary arteriography six months postoperatively revealed both ACSVG to be pa

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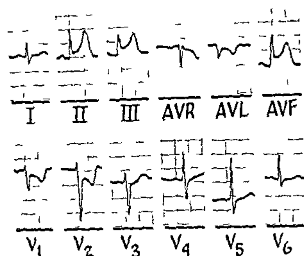


Fig 5A Patient 2 A 12 lead ECG demonstrating ST segment elevation in Leads II III and aV F during an acute episode of chest pain

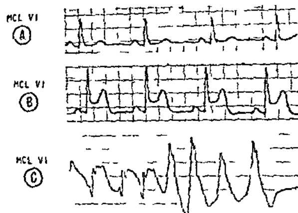


Fig 5B Patient 2 A MCL VI monitor lead tracing during an episode of chest pain demonstrates (*A*) patient's normal pattern (*B*) ST segment elevation and (*C*) short run of ventricular tachycardia



Fig 6 Patient 2 A right anterior oblique view (30 degrees) of the left coronary artery demonstrates high grade obstruction in the left circumflex coronary artery (LCX)

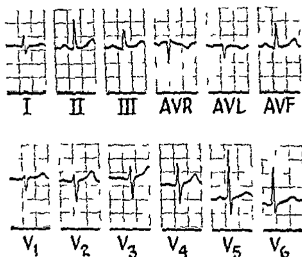


Fig 7A Patient 2 Two and one half years postoperatively the resting ECG was normal

operation without recurrent chest pain A recent resting ECG was normal and an exercise ECG was normal at a heart rate of 150 beats per minute (Figs 7*A* and 7*B*)

Discussion

Prinzmetal's variant angina is characterized as typical ischemic cardiac pain with the major exception that pain occurs at rest and not during exercise These episodes tend to be cyclic and may occur at approximately the same time daily [1,2] The ECG demonstrates ST elevation rather than depression in the distribution of the involved coronary artery [1,2] Approximately 50 per cent of patients with variant angina have ventricular arrhythmias and in a few patients atrioventricular block develops [1,2,4,6] The patients here reported had clinical features typical of Prinzmetal's variant angina

The prognosis of patients with variant angina appears to be poor In a recent review of 15 patients, four had myocardial infarctions averaging three months after the onset of symptoms and five patients died an average of 19 months after onset of symptoms [7] In Prinzmetal's series of 32 cases, 12 patients had myocardial infarctions and two patients died, presumably of arrhythmias [2]

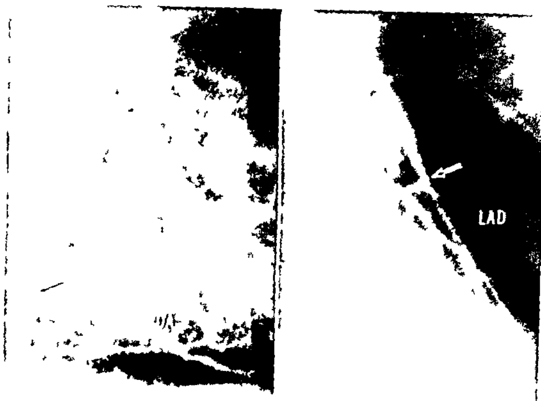


Fig 3 Patient 1 Right anterior oblique views (60 degrees) demonstrating (left) a patent graft to the posterior *descending coronary artery (PDA)* and (right) a patent graft to the left anterior descending (LAD arrows indicate site of anastomosis)

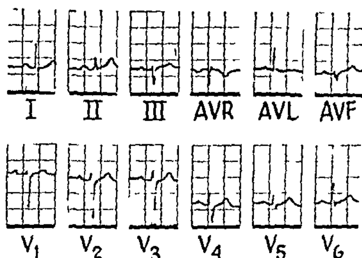


Fig 4A Patient 1 *Six months postoperatively the patient* had a normal 12 lead ECG

to 5 mg per minute Coronary arteriography revealed a 90 per cent obstructing lesion in the mid third of the LCX (Fig 6) The dominant coronary artery was the left There was also diffuse disease in the RCA Multiple x ray views of LAD were interpreted to be normal

At operation an ACSVG was inserted from the ascending aorta to the LCX Flow measurements were not made

The patient's postoperative course was unremarkable There were no further episodes of chest pain ST elevation or evidence of an operative or immediate postoperative myocardial infarction Two and a half years have elapsed since

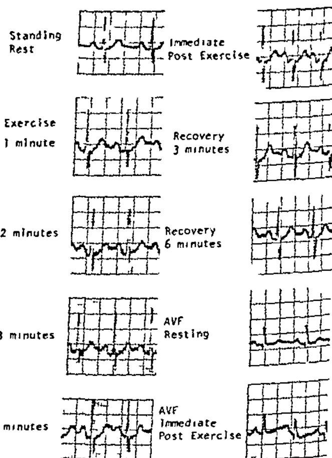


Fig 4B Six months postoperatively the patient had a normal exercise ECG at a heart rate of 140 beats per minute A Blackburn monitor lead system was used [15]

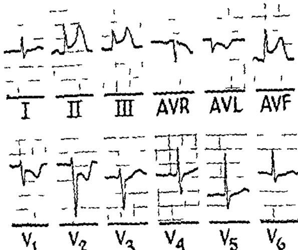


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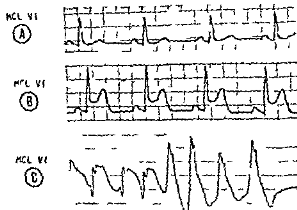


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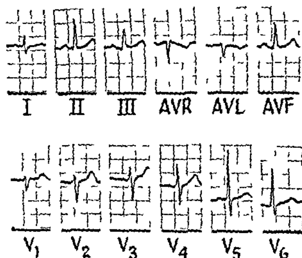


Fig 7A Patient 2 Two and one half years postoperatively the resting ECG was normal

atrioventricular block develops [1,2,4-6] The patients here reported had clinical features typical of Prinzmetal s variant angina

The prognosis of patients with variant angina appears to be poor In a recent review of 15 patients four had myocardial infarctions averaging three months after the onset of symptoms and five patients died an average of 19 months after onset of symptoms [7] In Prinzmetal s series of 32 cases 12 patients had myocardial infarctions and two patients died, presumably of arrhythmias [2]

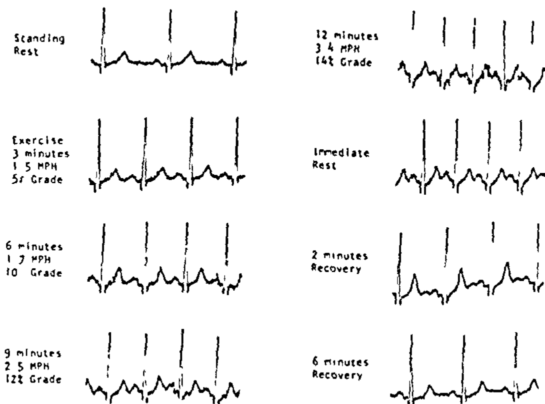


Fig 7B Two and one half years postoperatively an exercise ECG was normal at heart rate of 150 beats per minute

Although it has been suggested that variant angina may be associated with an isolated lesion in a single coronary artery a few autopsy studies have demonstrated diffuse coronary artery disease in addition to the high grade obstructing lesion [1,3] Both patients reported had significant lesions obstructing more than 50 per cent of the lumen in at least two vessels Patient 1 had disease involving all three coronary arteries The ST segment shifts and arrhythmias however are thought to be a consequence of a single high grade obstructing lesion [1,3] The hope that patients with variant angina might represent the ideal surgical candidate having an isolated solitary lesion in one coronary artery is not borne out in some instances

It has long been recognized that ischemia predisposes to ventricular irritability Recently experimental studies have helped to delineate possible underlying mechanisms Han demonstrated that the fibrillatory threshold in the ventricle is decreased during ischemia [8] Additional studies have demonstrated that ventricular impulses are propagated very slowly through ischemic areas and emerge into normal repolarized areas as re entrant beats [9] Such a re entrant process may continue to produce multiple extrasystoles or tachycardia in the ventricle Although difficult to prove it would seem that a re entrant mechanism secondary to ischemia may have been the basis for recurrent ventricular tachyarrhythmias in these two patients

Patients with recurrent ventricular tachycardia due to myocardial ischemia may note cessation of the arrhythmia after suffering a myocardial infarction Myocardial infarctions are common following saphenous vein bypass surgery [10] That such is not the situation in the patients reported here and that the relief from the arrhythmia was subsequent to relief of the ischemia by operation is supported by the normal postoperative ECG s in both patients and by the patent saphenous vein grafts in the first patient

The surgical approach for variant angina and ventricular arrhythmias is supported by the cases reported here and by several recent reports of patients with ischemic heart disease (not variant angina) and recurrent tachyarrhythmias who have noted abolition of arrhythmias following coronary artery surgery [11,12,14] It would appear that coronary artery bypass surgery may be of benefit to patients who suffer from recurrent tachyarrhythmias which are secondary to

ischemic heart disease and which are resistant to medical therapy by a reasonable outpatient regimen

Summary

Two patients with Prinzmetal s variant angina had recurrent episodes of resting chest pain ST segment elevation QRS widening ventricular tachycardia and ventricular fibrillation These episodes were unresponsive to medical therapy including lidocaine procaine amide and quinidine sulfate Coronary arteriography revealed severe obstructive coronary artery disease involving more than one coronary artery in both patients Aorticocoronary saphenous vein grafts were utilized to bypass significant disease in each patient In one patient blood flow through the grafts was measured at 90 and 65 ml per minute respectively at operation and patent grafts were demonstrated six months postoperatively Neither patient has had recurrence of chest pain or evidence of ventricular tachycardia at one year or 2½ years postoperatively Postoperative resting and maximal exercise ECG s are normal Coronary artery surgery may be an effective method of therapy for ischemic ventricular tachycardia when medical therapy fails

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Clinical pathologic conference

Marvin A Kirsh, M D
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John G Batsakis, M D
Ann Arbor Mich.

Clinical abstract

This 21 year old black male had a "heart murmur" since birth Except for occasional episodes of shortness of breath with exercise, he was relatively asymptomatic during his childhood and adolescence At 17 years of age he was admitted for preoperative cardiac catheterization because of increasing fatigue and dyspnea

Catheterization studies (Table I) demonstrated systemic pressures in the right ventricle with evidence of only infundibular pulmonary stenosis on the pullback tracing A cine angiocardiogram demonstrated a moderately sized ventricular septal defect with bidirectional shunting as well as the infundibular pulmonary stenosis Surgical correction was recommended, but this was refused by the patient

Over the next four years, the patient s symptoms progressed to the point where he required hospitalization again at the University of Michigan Medical Center

Physical examination revealed no retardation of growth His pulse rate was 40 per minute Chest examination revealed a right ventricular precordial heave accompanied by a Grade V/VI harsh holosystolic murmur which was loudest in the second and third left intercostal space The second sound was single A Grade II/VI apical diastolic murmur was also audible Femoral pulses were symmetrical and there was no cyanosis or clubbing

The electrocardiogram indicated (1) right ventricular hypertrophy (2) nodal sinus bradycardia with nodal or ventricular escape beats and (3) an intraventricular conduction defect in the right bundle Chest x rays taken at this time, are shown in Figs 1 and 2 Clinical laboratory studies included a hematocrit of 52 and hemoglobin of 16 1 Gm per 100 ml

He underwent a corrective cardiac operation No untoward complication occurred during the operation or during the first 48 postoperative hours On the morning of the third postoperative day, while the chest tubes were being removed, laceration of the right atrial appendage occurred with exsanguination cardiac arrest, and death

Of historical interest was the fact that one of his seven siblings had died at age 27 years, of cyanotic congenital heart disease

Discussion

DR KIRSH The clinical features roentgenographic findings and cardiac catheterization data are all consistent with the diagnosis of tetralogy of Fallot Of particular interest is the patient's age and the family history Survival of patients with *acyanotic* congenital heart disease until middle and late adult life is now well recognized Such longevity in patients with *cyanotic* congenital heart disease is much less frequent but tetralogy of Fallot is one form with which patients may survive into early adulthood Although the average life span of a patient with an uncorrected tetralogy is 12 years it has been estimated that nearly 10 per cent of children with this lesion survive up to 21 years

Approximately 35 patients older than 40 years with surgically uncorrected tetralogy of Fallot have been reported in the literature four of these patients have lived to their seventh decades A long survival is probably in part related to an anatomic defect that initially results in a mild hemodynamic derangement Additionally the development of a bronchial collateral circulation results in a physiologic compensatory response that tends to favor survival Bing, Vandam and Gray[1] have shown that pulmonary capillary flow greatly exceeds pulmonary arterial flow in patients with long standing

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Fig 1 Preoperative chest roentgenogram showing cardiomegaly with enlargement of the right ventricle Pulmonary vascular markings are slightly increased The top arrow points to the dilated azygos vein the bottom arrow points to the stomach bubble beneath the right diaphragm



Fig 2 Preoperative lateral chest roentgenogram exhibiting an absence of the inferior vena cava shadow behind the heart

Table I

Catheter position	Pressure (mm Hg)	Oxygen saturation (%)
Superior vena cava		75
Inferior vena cava		73
Hepatic vein		68
Mid right atrium	(Mean 13)	75
Low right atrium		75
Low right ventricle		75
Mid right ventricle	140/20	86
Central pulmonary artery	30/13 (Mean 19)	78
Left pulmonary artery	35/13 (Mean 20)	79
Right pulmonary artery	30/13 (Mean 19)	79
Left pulmonary artery wedge	(Mean 17)	
Right pulmonary artery wedge	(Mean 18)	100
Left ventricle	130/85	97
Ascending aorta	130/85 (Mean 100)	
Brachial artery	130/85 (Mean 102)	97

tetralogy As the result of a gradual progression of right ventricular outflow obstruction caused by an increasing infundibular muscular hypertrophy and endocardial fibrosis a clinical deterioration occurs during adulthood This is characterized by decreasing exercise tolerance dyspnea cyanosis, and syncope

If there is an optimal relationship between the size of the ventricular septal defect and the degree of pulmonary stenosis an acyanotic survival into adulthood is possible As manifested by this patient the majority of such subjects have a *relatively asymptomatic early youth* but become symptomatic as they enter the third or fourth decade of life Exertional dyspnea and exercise intolerance are the principal symptoms [2]

The roentgenographic appearance of this patient s heart demonstrates a cardiomegaly whose configuration suggested right ventricular enlargement Pulmonary vascularity appears slightly increased. On lateral chest x ray the inferior vena cava shadow normally present *posterior to the heart*, is absent. Other findings of note include the presence of a markedly dilated azygos vein and the presence of a gas shadow under the right hemidiaphragm (Figs 1 and 2) These findings in combination are very suggestive of an anomaly of the abdominal inferior vena cava At the time of cardiac catheterization injection of contrast medium into the right atrium yielded an opacification of the hepatic vein but no opacification of the inferior vena cava below the hepatic veins To clarify this find

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among *siblings* of patients afflicted with tetralogy of Fallot in Nora s series was 2 7 per cent Similar statistics have been reported by others Among 100 families of children with tetralogy studied by Boon [5] eight showed a relative with tetralogy and 16 showed a relative with other congenital heart lesions No chromosomal defect has been identified to account for this rather striking correlation

DR. SODEMAN Postmortem examination revealed an enlarged heart which weighed 870 grams There was a fibrinous epicarditis with hemorrhage into the mediastinal soft tissue The cardiac malformations were those of a tetralogy of Fallot and consisted of (1) a 25 by 20 mm ventricular septal defect in the membranous septum which was closed by a Teflon patch (2) right ventricular hypertrophy (11 mm) with moderate chamber dilation (3) infundibular stenosis in the mid and lower portion of the infundibulum relieved by operation (4) dextroposition or over riding of the aorta consistent with a Spitzer type I defect In addition the right atrium was dilated and the crista supraventricularis displaced anteriorly The aorta arched left and there was a slight enlargement of the aortic ring The left atrium and ventricle were unremarkable No atrial septal defect was found. Surrounding the repaired ventricular septal defect there was hemorrhage in the myocardium with focal necrosis As Dr Kirsh outlined, there was an anomalous venous return The abdominal organs did show situs inversus with a reverse rotation of the intestines The appendix was in the right lower quadrant and the transverse colon posterior to the small bowel

On microscopic examination there were hepatic changes of chronic passive congestion with early fibrosis around the central veins A portal infiltrate with fibrosis in the portal area suggested chronic persistent hepatitis There was pulmonary edema with moderate congestion of the alveolar capillaries The pulmonary micro vasculature was unremarkable and no micro thrombi were present

I would like also to review his brother s history and necropsy His brother was 27 years old when he was admitted to the University Medical Center and presented with a similar clinical history of a murmur since birth without significant symptoms until three years before death He entered the hospital because of a marked increase in fatigue shortness of breath and ankle edema Phlebotomy was undertaken because of a severe secondary polycythemia Over the next four days he experienced repeated syncopal episodes During one of these he aspirated, had a cardiac arrest and died.

His heart was enlarged weighing 570 grams The right ventricular myocardium was hypertrophied and the atrial and ventricular chambers dilated. There was infundibular stenosis of the pulmonary outflow tract. A well developed conus was present with no fibrous continuity between the pulmonary and mitral valves The aortic and mitral valves were also separated by a second well developed conus The aorta arose posterior and to the right of the pulmonary artery Both had their origin in the right ventricle

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Fig 3 Inferior vena cavagram demonstrating an interruption of the inferior vena cava above the renal veins with azygos continuation of the inferior vena cava

ing an inferior vena cavagram was performed (Fig 3) This demonstrates an abrupt and oblique interruption of the inferior vena cava just above the renal veins at a point where the hepatic veins normally should enter A second injection shows continuation of the inferior vena cava into the azygos vein Barium studies of the upper gastrointestinal tract demonstrate a situs inversus or at least a right sided stomach

This anomaly represents interruption not absence of the inferior vena cava The infrarenal segment is normal and the inferior vena cava stops just above the renal veins Blood continues to the heart in the azygos or hemiazygos system The suprahepatic segment of the inferior vena cava is composed of the confluence of hepatic veins The incidence of this peripheral venous anomaly in patients with congenital heart disease has been estimated to be from 0 6 per cent to 1 0 per cent Nearly one half of these patients also manifest abnormalities of abdominal situs inversus which include malrotation of midgut foregut, and/or colon

The associated cardiac abnormalities have most often been truncus arteriosus pulmonary stenosis A V comunis and transposition of the great vessels

Prominence of the azygos vein should alert the surgeon to the possibility of the above venous anomaly so that different cannulation techniques may be used to obtain an adequate venous return during open heart surgery

At the time of operation the patient's right atrium, especially its appendage was markedly enlarged Because of the interruption of the inferior vena cava three separate canulae were inserted via the right atrium into the hepatic veins azygos vein, and the superior vena cava This provided adequate venous drainage A vertical right ventriculatory incision was used to expose the outflow tract where the pulmonary stenosis was infundibular Enlargement of the right outflow tract was obtained by excision and incision of the muscle from the medial and lateral walls excision of the fibrous tissue along the leading edge of the crista supraventricularis, and division of hypertrophied trabeculae carnae The ventricular septal defect (25 by 20 mm) was closed with a Teflon patch Following the cardiopulmonary bypass there was only a 30 to 40 mm gradient across the outflow tract The immediate postoperative course was uncomplicated suggesting the pulmonary vascular bed was able to accommodate a normal flow of blood.

The successful corrective surgery was fatally marred by the laceration of the right atrial appendage on removal of a chest tube. This is an extremely rare postoperative complication and is the first in over 3 000 open heart operations performed at our institution

Although the outcome in this patient was not successful complete correction should be offered to all patients with tetralogy of Fallot. In almost all patients their cyanosis disappears and a normal exercise tolerance is achieved No other form of management should be considered in the older patient provided there is an adequate pulmonary bed The operative mortality in older subjects is no greater than that accompanying surgical correction in the young and the long term results closely parallel those attained in the pediatric age group [3]

DR BATSAKIS The sibling s cardiac disease is of some interest It is now well established that there is a striking familial aggregation of congenital heart disease Nora s[4] survey of families with congenital heart disease indicated that 34 per cent of 417 randomly selected patients with cardiac anomalies also had one or more relatives with an established diagnosis of congenital cardiovascular malformations In a matched control group only 9 per cent of families gave positive histories

The frequency of congenital cardiac lesions

onary patients those in the fourth decade were consistently described by the nurses as being overly cheerful jovial manic flirtatious and seductive whether verbal or motor their communications centered on their masculine attractiveness Uncertainty was the issue raised most during psychological interviews[15]

What is the patient to do? A publication of the American Heart Association directed to the lay public states This question (postmyocardial infarction sex activity) frequently worries patients a good deal and it is wise for them to discuss it with their physician[16] But exactly how much does the physician know about this topic and how willing is he to discuss it?

At a cardiac work evaluation clinic two thirds of the men who had had myocardial infarctions one to nine years earlier reported that they had been given no advice regarding sex activity while the other one third described physicians as giving only vague and nonspecific advice[13]

In a Boston Veterans Administration study including 307 patients and 102 physicians the interrelationships between sex and illness were evaluated[17] The patients perceived the doctors as initiating discussions of sex far less frequently than doctors thought they did, both agreed that patients seldom initiate discussions of sex unless they have psychiatric problems Physicians believe circulatory disorders are the second most common catalysts of sexual discussion but patients view circulatory ailments as very minor topic initiators Of the 112 patients reporting discussion of sexual matters (initiated by either patient or doctor) 44 per cent believed such discussion is helpful cardiovascular patients comprised the second largest number of this group

The strong influence of a physician's opinion on patient attitudes and function demands of him the elimination of anxiety fear or depression As one observer points out expression of such feelings (fear of sex) by the patient should not be followed by the doctor's admonition don't worry but rather an acceptance of these feelings as legitimate and important[12]

Most physicians simply give general advice shifting the ultimate decisions to their patients This is hard for the patient who is looking for strict rules to follow Physicians respond to their own uncertainty in two ways—conservatism or avoidance[12] The former approach restricts activities while the latter results in no discussion or ambiguous responses such as do what you feel like doing Both situations lead to decreased sexual activity which may be physiologically unwarranted and psychologically detrimental

Before 1956 there were only two documented studies of human physiologic response during coitus according to Bartlett[18] who in that year studied the heart rate and pulmonary ventilation during intercourse Significant was his finding that heart rate accelerated nearly 100 beats per minute in as little time as one minute *with an equally brief* postorgasm return to normal

The heart rate phenomenon has significance for the cardiac patient because of increased oxygen demand In addition some believe that the alkalosis from hyperventilation may aggravate ischemia by reducing the amount and rate of oxygen release secondary to shift of the hemoglobin oxygen dissociation curve[19]

For all practical purposes these two points with their negative overtones are all that many physicians know about sexual activity and as a result conservative advice is prescribed

The questions then that need answering include the following Does sexual activity produce significant strain? What is the magnitude of the metabolic load placed on the heart? Can strain be modified by drugs or varied sexual techniques and if so how? Most important how does the cardiovascular cost of sexual activity compare with that of other daily living activities? The goal of answering these questions is to determine the basis for counseling the individual patient to return to an active sexual relationship[1]

Before continuing some basic physiologic concepts must be presented. The cardiac demand or oxygen consumption of physical work depends upon the work performed. Therefore the physiologic demands of any physical activity can be estimated by oxygen or caloric consumption An important parameter in assessing fitness is the maximal oxygen intake

Since a direct measurement of maximal oxygen intake can be made only in special laboratories and maximal tests are not advisable for older people generally and cardiac patients in particular a method of testing was devised whereby submaximal workloads could be used to estimate maximal oxygen capacity and thus physical fitness From the Astrand and Rhym

Sexual activity and the postmyocardial infarction patient

Andrew W Green M D
St. Louis Mo

Rehabilitation has the goal of restoring an individual to his optimal status in physiologic, psychologic and vocational terms The literature is extensive in explaining the broader aspects of postmyocardial infarction rehabilitation but a scarcity of material exists with regard to their sexual rehabilitation

Hellerstein and Friedman[1] in one of the most comprehensive articles to date on this subject reported that a review of 33 cardiology textbooks found less than 1 000 words referring to sexual activity and heart disease Even the Journal of Rehabilitation s extensive 40 article review on coronary management failed to discuss sexual activity[2-6]

The noted sex researcher Dr William Masters states that he has 'not had the opportunity to work in this field to any significant degree'[7] and no studies have dealt with sexual activity in animals with naturally occurring or experimentally induced heart disease

Most articles simply discuss isolated anecdotal reports experiences and impressions these always emphasize the need for specific studies in view of the increasing attention being focused on cardiovascular disease

That a problem exists for the coronary patient is exemplified by group therapy reports in which convalescent male cardiac patients express feelings of diminished libido fear of death during intercourse and an anxiety that exists at a preconscious level for many years—a feeling shared by spouses[8, 9] Hesitancy to ask for a physician's advice is also common because of their fear of sexual restrictions

One sex researcher noted that the postmyocardial infarction patient is fearful of sexual relations despite all reassurance that sex is medically permissible The alteration in sexual function may reveal itself in diminished interest and frequency, impotence, or hypersexuality, but the fear response usually dominates and may become a phobia[10] Furthermore, one psychiatrist noted sexual problems to be more common in coronary patients[11]

Alteration in postmyocardial sexual function has been documented In a study of 20 myocardial infarction survivors interviewed from three months to four years after injury only five reported full resumption of sexual activity seven claimed complete abstinence and eight characterized their sexual activity as being diminished[12] A work evaluation clinic review indicated that only one third of the postinfarction patients returned to normal sexual activity and two thirds had a marked and lasting decrease in frequency of intercourse to below 50 per cent of their premyocardial infarction state 10 per cent became permanently impotent[13] Change in behavior was usually by the patient s own choice based on misinformation and fear

The most common misconceptions of coronary patients include the belief that even mild exertion kills sexual intercourse should never again be attempted and repeat infarctions tend to occur at orgasm[14]

In actuality the problem surfaces in the hospital The inability of patients to comply with the hospital regimen a routine occurrence in any coronary care unit represents an emotional response to the coronary diagnosis In a psychological evaluation of 30 hospitalized male cor

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ing[20] nomogram for calculation of aerobic capacity, one can determine maximal oxygen in take in liters per minute simply from a knowl edge work level performed

Other parameters used include the workload (WL)-150 or the work load necessary to elicit a heart rate of 150 beats per minute, the HR × SBP 25,000, or the work load necessary to elicit a heart rate times systolic blood pressure product of 25 000, and the *met* where the *met* equals the energy expenditure per kilogram of body weight per minute of one average individual sitting in a chair or lying at rest (the heart rate correlates well with the number of *mets*)

All four of these parameters appear in the lit erature and are used in a determination of physi cal fitness by different authors but in general most conclude that heart rate is a very practical measure of oxygen consumption and, thus physi cal work Although many believe that blood pressure is an important parameter its signifi cance has been questioned because of the in creased disparity between aortic and radial pulse pressure during exercise [?]

Hellerstein s study observed patients in daily living activities and during coitus This study used a questionnaire survey and electrocardio graph monitoring of 101 men randomly selected from the Case Western Reserve University physi cal fitness evaluation program Forty eight pa tients were postacute myocardial infarction and 43 cases were normal subjects but highly coro nary prone based on criteria which indicated in creased susceptibility to premature development of coronary heart disease (increased serum cho lesterol hypertension obesity, smoking and decreased physical activity) Included was a sub sample of 14 subjects engaged in conjugal sexual activity during the monitoring period

The heart rate and electrocardiogram changes associated with sexual activity were compared with those occurring in other activities of the 24 to 48 monitoring hours These heart rates were then compared with those obtained during bicy cle ergometer exercise performed within several weeks of sexual study The object was to equate that amount of muscular work (kilopound meters per minute oxygen uptake per kilogram of body weight) with a particular heart rate

The mean maximal heart rate during sex cor responding to phase of orgasm was 117 4 (range 90 to 114) with the average heart rate for the period two minutes before to two minutes after maximum heart rate being 97 5 (range 85 0 to 102 2)

The oxygen uptake (in terms of per cent of maximal oxygen consumption as determined by bicycle ergometry) was 60 3 per cent (16 0 ml of O_2 per kilogram) for the maximum heart rate and 45 3 per cent (11 9 ml of O_2 per kilogram) for the average heart rate It should be noted that the average Master two step test requires 22 3 ml of O_2 per kilogram (Hellerstein s program ad vises exercise at 60 to 70 per cent of maximum oxygen capacity for 20 to 30 minutes once every two to three days)

The mean maximal heart rate during usual work was 120 1 (range 101 to 130) Of the 14 pa tients on the monitor six patients had a max imum heart rate at sex of 127 and at work of 117 The other eight patients had a maximum heart rate at sex of 110 and at work of 120 The work activity producing this rate included walking climbing stairs and doing paper work

Electrocardiogram changes were also noted during the monitoring time although some believe the Holter monitor to be of value only for rate, rhythm, and conduction pattern analysis with ST and T wave changes being interpreted with caution because of distortions in the record ing system and changes in positional activity [22] During sex four patients had ST T depression (three showed similar changes at work) and three patients had ectopic beats During the work phase, four patients exhibited ST T changes (three patients had similar changes dur ing coitus) and five patients had ectopic beats

From the above data Hellerstein concluded that the cardiovascular responses (ST changes and ectopic beats) *during coitus and normal oc cupational activities were comparable in fre quency and severity*

The average man who has recovered from an uncomplicated myocardial infarction has a max imum capacity of eight to nine mets [19] The max imum heart rate activity during coitus is approxi mately five mets for less than 30 seconds During pre and postorgasm periods the energy cost is about 3 7 mets (In calories this is 6 cal per minute for less than 30 seconds during maximum sexual activity with 4 5 cal per minute during the pre and postorgasm period)

Although the heart rate is a crucial determina tion of myocardial oxygen demand the duration

of such sustained increased heart rate is important The concept of the long drawnout Hollywood like amorous fits of sexual ecstasy evoking physiologic responses of an Olympic relay race was disputed by Hellerstein His questionnaire revealed these facts the average middle aged man engages in sex twice per week comprising less than 0 3 per cent of leisure time the average time to maximum heart rate after retiring to bed is 16 3 minutes (10 to 30 minutes) 74 per cent of cases average less than 10 minutes from beginning of intromission to male orgasm

Thus the time and energy cost of sex is relatively benign If the cardiac patient can walk on a treadmill at three to four miles per hour climb stairs or pass a Masters test without undue increase in blood pressure heart rate or electrocardiogram changes his exercise capacity is five to six mets and is therefore above the work requirements of sex [19] One seminar[23] went so far as to say that if a patient can perform at a level of six calories per minute or do 600 kg per minute on a bicycle ergometer or just climb one or two flights of stairs then sexual activity is permissible

The implications of these data are straightforward. In order to pursue sexual activity safely the heart must be trained to tolerate a specific work load. Hellerstein with more than 20 years of experience in this field,[4 4 28] *explains that the* physically fit individual can perform a given level of work at a lower heart rate and lower systolic blood pressure than can the unfit person Furthermore the trained individual has the capacity to raise his heart rate to higher levels.

No sophisticated equipment is necessary to evaluate fitness even if a bicycle ergometer or treadmill is unavailable A step test is adequate enough so is observing the performance of walking or climbing stairs followed by measuring the heart rate and recording an electrocardiogram. Once fitness is determined (by indirectly evaluating maximum oxygen capacity as reflected by heart rate response to exercise) a program can be formulated to improve the patient s fitness so that normal activities including sexual intercourse can be performed safely

The doctor must remember that enough objective data are available and that much can be gained by noting the patient s response to simple activities. Furthermore the doctor s knowledge of the effect of temperature of eating and drinking and of tension and fear on the cardiovascular system supplement his ability to advise the patient objectively

That participation in an active program has physiologic benefits has been well documented in the literature Hellerstein s study assessed sexual activity changes in those subjects who participated in the physical fitness program Although most subjects reported no change in frequency or quality 67 per cent of the initially symptomatic subjects reported few or no symptoms with sex after exercise reconditioning

The wives of the subjects were enthusiastic about the program as well because of the change in personality and the greater ease of cohabitation Common postmyocardial infarction depression also was much less severe

One pertinent question is whether sex could be used as one of the exercise methods since it is considered to have a specific energy cost like jogging Hellerstein responded to this question at a seminar by explaining that sex, unfortunately is too brief to be effective for improvement since he exercises his patients for 30 to 60 minutes per session Although he admits that 15 to 30 minutes per session would probably be equally effective if one can find a middle aged bed athlete who can do this I agree that it would be a fine way of physical conditioning [23]

The subject of sudden death during coitus deserves attention because of its great concern to doctors and patients The Japanese[23] report 0 6 per cent (34 out of 5 559) incidents of death during *coitus in cases* of endogenous sudden death Eighteen out of 34 coital deaths were attributable to heart disease with 27 out of 34 deaths occurring during or after extramarital intercourse Hellerstein from a personal communication with a coroner estimated coital death in only three of 500 atherosclerotic heart disease subjects

More data are needed (as is exemplified by a coital coronary questionnaire[30]) although it is difficult to refute one coroner s observation that acute coronary insufficiency resulting from coitus is a fact," but the causal relationship of coitus to sudden death is still a matter of relative probabilities rather than absolute proof [31]

Some believe that the powerful pressor effect of emotion can be a causative factor in unexpected death How this relates to the cardiovascular system is the subject of work by Wolf [32-33] and others [34 35] Physiologically emotional stress

inhibits adaptation to exercise, alters renal salt and water excretion (possibly contributing to increased blood pressure), and may alter renal blood flow to increase blood viscosity—all causing increased cardiac work

One study reproduced ST T changes of a Master two step test by subjecting patients to an emotional psychologic interview [37] Stress has also been shown to stimulate high serum cholesterols

How this relates to coital death is put in perspective by one medical examiner, who noted that Death in the Saddle follows a pattern [31] The deceased is usually married he is with a nonspouse in unfamiliar surroundings after a big meal with alcohol Taking these factors into consideration Massie in this article, discourages extramarital liaisons Most patients are safe if they perform the act judiciously '

A study indirectly related to the coital coronary analyzed factors at the onset of coronary occlusion and coronary insufficiency [38] Of 1 347 attacks of coronary occlusion 30 per cent occurred at rest 23 per cent at sleep and 8 7 per cent during moderate activity which included coitus Concerning coronary insufficiency (defined as prolonged angina resulting in necrosis or infarction), the statistics revealed 56 per cent occurrence at rest or during mild or moderate activity and 49 per cent under medical conditions of decreased coronary flow This study concluded that coronary insufficiency is more common and is associated with a precipitating factor in one third to one half of the cases whereas occlusion occurs with unusual exertion in only 2 per cent of the cases

Keeping these data in mind and the fact that only 2 per cent of one s day is spent in acute effort and one third to one half of the day involves mild to moderate effort (the sex act included) worry over a coronary occlusion only during coitus alone seems unjustified although coronary insufficiency is a possibility but justifying no greater concern than should most routine activities

What do doctors advise now that we have shown that there is enough information to formulate a decision and that advice is sometimes given? One Texas cardiologist reported that 90 per cent of his colleagues counseled patients on sex [23] Eighty three per cent suggested limited sex activity 50 per cent suggested abstinence for two weeks to three months (an average of six to eight weeks), and 13 per cent advised unlimited sexual activity Seventy per cent believed that sudden death is a realistic possibility 31 per cent stating that they would advise their patients of this danger

Hellerstein received questionnaires from 2 054 physicians Ninety four per cent said they counseled on sex using clinical judgment and tolerance of daily activities (87 per cent) or functional capacity by standard exercise testing (18 per cent) [1] Again one must question the accuracy of these data in light of the patient s perception of whether advice is given

Other advice tends to include these items[39] eight weeks of no activity because of a healing myocardium, eight to twelve weeks of moderate restraint in sex with limited frequency and duration no sex postprandially no alcohol, no amphetamines and hallucinogens avoid an atmosphere of tension pressure or haste complete abstinence if symptoms of heart failure or angina occur prophylactic nitroglycerin avoid too great excitement and normal activity during the chronic rehabilitation stage

The truths and fallacies of these opinions, in light of the ideas already presented are obvious Limitation of sex activity for eight weeks is debatable Until the patient s exercise tolerance is assessed sexual abstinence is advisable, but eight weeks is not a firm figure Since many hospitals have rehabilitation exercise programs for uncomplicated myocardial infarctions requiring patients to walk 2 500 feet and up two flights of stairs by four weeks without a significant heart rate increase sexual activity would seem to be permissible Thus each patient must be evaluated in terms of his own activity response

Nitroglycerin is useful if the patient becomes symptomatic but, again an adequate exercise program to increase tolerance so that sex activity is below the tolerance level should be instituted.

Avoidance of sexual excitement is prescribing what Massie calls sedate coitus in a healthy marital atmosphere with full partner cooperation One step lower is moderate coitus ' or enough to satisfy the emotional and physical needs of the partners [31] However all this seems unnecessary because sex is probably un olympic like in most middle aged couples eliminating the need for married patients to be told of time and number limits Should this not be the case such restrictive advice may be beneficial

only if the patient is in poor physical condition Regarding advice about myocardial stimulants and postprandial stress this seems physiologically sound as is the advice about tension pressure and haste

However one should remember who is being advised because instructions that go beyond the actual activity of the patient may unnecessarily alarm him Advice pertinent to the patient is the key

All of this emphasizes consideration of the variables in evaluating a patient s sexual response to disease such as the premorbid state of the individual the physiopathologic effect of the disease process the psychologic state of the patient the effect of treatment upon the patient and, the response of the marital partner to the illness [10]

One fault in this discussion has been the lack of reference to the female Probably the decreased incidence of literature referral prompted this unfortunate situation However most female coronary patients are in an age group where sexual activity is supposedly less although this too is in dispute

The importance of the female must not be ignored because she is very significant in this sexual problem Many females fear their partners health situation and avoid sex Because of this fear and the doctor s advice to shift the sexual aggressiveness to the female (if it is not already there) she is thrust into a psychologically traumatic situation The fears of the wives may be displaced into avoidance of sex, overprotection or resentment, leading to a situation that is more detrimental than the underlying pathology [5,10] Hellerstein[4] notes the importance of explaining the restrictions and capacities of the patient to the wife Any misconceptions should be sought out and corrected during this discussion

Thus one can conclude from the material presented that sex is on the mind of the coronary patient from the onset of his illness that discussion of sex should be initiated as soon as the patient is stabilized that a communication gap does exist between the doctor and the patient that an information gap exists also for the physician that improper advice may result from this lack of information that misinformation can be detrimental to the patient that physiologic data are sufficiently available however to reach fairly safe conclusions about sexual activity tolerance of the coronary patient that exercise rehabilitation facilitates tolerance of sexual activity improving both physiologic and psychological recovery that there is little reason to deny the coronary patient a healthy sex life that there is insufficient data to alarm the patient and the physician of sudden coital death that the type of advice should be based on a knowledge of the patient s precoronary sexual activity his marital relationship other psychological factors and his cardiovascular medical status that the spouse should be involved in a discussion of the topic and finally short term psychotherapy is a useful adjunct to the management of the myocardial infarction patient

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Electrophysiology and pharmacology of cardiac arrhythmias III The causes and treatment of cardiac arrhythmias Part B

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Clinical pharmacologic considerations

Even when selection of an antiarrhythmic drug is correctly based on an understanding of the electrophysiologic basis for the abnormality to be treated and the actions of the drug in relation to the existing abnormality the success or failure of treatment depends strongly on other considerations Paramount among these is an understanding of the therapeutic range of plasma levels for the drug selected and the rules governing its absorption distribution metabolism and excretion

No therapeutic effect is evident for most drugs until a sufficient concentration is attained in the blood or plasma Although one would like to know what the drug concentration is at its site or sites of action this information is not available We must assume therefore that the plasma level reflects it in a predictable way Also if the concentration of drug is excessive toxic effects appear For a given drug one thus can define ranges of concentrations or plasma levels within which one can expect the drug to exert its desired and its toxic actions in most patients The limits to these ranges are not absolute because there is variability between patients and in a given patient with time Nevertheless, in terms of prior experience it is permissible to define a *minimum* effective concentration (MEC) and a *toxic* concentration (TC) (Fig 4) and to assume that if the plasma level is maintained between these values the desired effects will be obtained.

The problem is to bring the plasma level *into* this range reasonably promptly and to *maintain* it there for the period of treatment. Ideally the mean *steady state* level should remain as far from the toxic concentration as will provide adequate control Also since the sensitivity of the arrhythmia to the drug may change from time to time *appropriate* adjustments in the plasma level may be necessary

If one considers first only the *maintenance* of a desired plasma level under steady state conditions there are two significant variables the rate of administration and the rate of elimination The rate of administration (either by intravenous infusion or repeated injection or oral administration) and the rate of elimination (either by metabolism, excretion or both) are the determinants of the total body store This vaue and the distribution of the drug within the body determine the plasma level. Whenever the rate of administration (or input) exceeds the rate of elimination (or output) the total store and plasma level will increase When the output exceeds input the reverse will be true and when the two rates are equal the total body store and plasma level will remain constant

It thus would appear that a knowledge of (1) these two rates (2) the distribution of the drug within the body and (3) body size would permit one to select a dose and dosing interval, or infusion rate appropriate to maintain any desired plasma level In many cases this is true but other factors may play an important role Both absorption and elimination of most antiarrhythmic

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An example of this is shown diagrammatically in Fig 6 Immediately after injection the plasma level is very high (indeed, often well above the threshold for toxic effects) Typically the plasma level first falls rapidly due to redistribution and then more slowly due to elimination It is important to remember that only free (unbound) drug diffuses across the capillaries For this reason if the drug is bound in large quantity to plasma protein the plasma level (of total drug) will remain much higher than if protein binding is minimal If the drug is bound in large quantity at extravascular sites (which may be *on or within* cells) the plasma level will be *proportionately* lower Thus much of the drug may remain within the vascular compartment or most of it may leave the vascular compartment promptly To estimate this tendency and thus the plasma level which can be expected to result from a single intravenous dose the concept of the apparent volume of distribution (AVD) has been employed The AVD is the plasma concentration divided by the dose

$$\frac{mg\ /ml}{mg} = ml$$

The plasma concentration can be obtained directly if after an initial rapid decline the plasma level changes only very slowly More frequently it is estimated by extrapolation as shown in Fig 6

There are some practical points to make in relation to the simple system diagrammed in Fig 6 In many instances the drug may distribute rapidly to some and less rapidly to other parts of the body In this case the change in plasma level with time will not be represented by only two exponential processes one representing distribution and the other elimination but rather by a curve reflecting distribution of drug among several compartments For the ideal system diagrammed, the initial rate of decline in plasma level represents also the rate at which drug concentration increases at its sites of action in the heart In reality this probably is an oversimplification and for many drugs the concentration at sites of action in the heart may increase much more slowly than the initial rapid fall in blood level This may be a problem of some magnitude when parts of the heart are poorly perfused

The extent to which the drug in the vascular compartment is bound is important not only in relation to the interpretation of plasma levels but

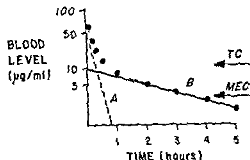


Fig 6 Schematic representation of the time-course of change in blood level of drug administered by a single intravenous injection and eliminated by a first order process. Note that levels are plotted on a logarithmic scale The interrupted curve and dots show the actual blood levels at different times The solid line (*B*) shows the exponential decline of blood levels due to elimination and the dashed line (*A*) shows the rapid decline due to redistribution Extrapolation of curve B to zero time gives the value of blood level used to estimate the apparent volume of distribution

also in relation to the intensity and duration of drug action Only free unbound drug equilibrates between blood and body A high plasma level of a drug which is in large part bound to protein may have the same effect as a lower level of a drug which is bound less extensively This is familiar in terms of plasma levels of digitoxin and digoxin Only free drug is excreted by glomerular filtration protein binding thus will retard excretion of some drugs Finally the binding sites are a variable reservoir for the drug changes in pH may increase binding and decrease the level of free drug while administration of another agent may displace any antiarrhythmic drug from its binding sites on plasma protein and thus intensify its action

Most commonly used antiarrhythmic drugs, with the exception of lidocaine are administered *orally in repeated doses* In this case the time course of the plasma level, as well as the mean value of the plasma level under steady state conditions will depend on the rate constant for both absorption and elimination the dose and the dosing interval Clearly there are many variables involved and changes in each can occur It is possible nevertheless to formulate some general rules which hold true for typical conditions (Fig 4) For any drug when it is administered in fixed doses at regular intervals if absorption is more rapid ($t_{½}$ shorter) the plasma level will rise more rapidly and reach a higher peak value if absorption is delayed the opposite will occur For any given rate of absorption (as described for constant intravenous infusion) the $t_{½}$ for elimina

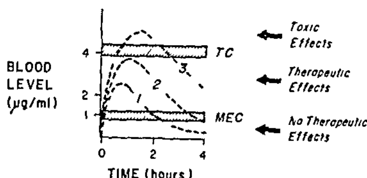


Fig 4 Schematic representation of the relationships between plasma levels and the minimum effective concentration (MEC) and toxic concentrations (TC) for a drug A single dose of drug is given by mouth at zero time and the interrupted curves 1 2 and 3 show the effect on the rate of change and magnitude of blood level of a progressive decrease in the rate of elimination.

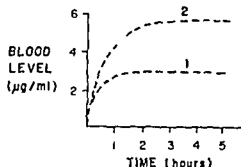


Fig 5 Schematic representation of the time course of the change in blood level of a drug administered by a constant rate intravenous infusion Note that if the rate of elimination is decreased (curve 2) not only is the steady state blood level increased but also the time required to attain a steady level is increased

drugs follow what are called first order kinetics For such drugs a constant fraction of the dose is absorbed per unit time and a constant fraction of the amount of drug in the body is eliminated in each unit of time These processes are described in terms of rate constants or more frequently by the half time ($t_{½}$) for absorption or elimination The $t_{½}$ measures the time required for 50 per cent of the dose to be absorbed or 50 per cent of the body store to be eliminated

It is important to remember however that not only is the rate of elimination one of the two determinants of the steady state drug level but also it is the *unique* determinant of the rate at which a given steady state level is attained These principles are demonstrated most simply by considering first the case in which the drug is administered by a constant intravenous infusion (input rate controlled) We can assume that all the administered drug remains within the vascular compartment and thus only elimination follows first order kinetics

This example is shown diagrammatically in Fig 5 When the drug is administered at a constant rate, if there were *no* elimination, the plasma level and body store would increase linearly with time However because elimination does occur, and because the amount eliminated per unit of time is a function of the concentration the rate of elimination will increase as the plasma level increases until the rates of elimination and infusion are equal When this condition obtains, the plasma level remains constant. If the rate constant for elimination were to change both the steady state plasma level and time required to attain that level would change (Fig 5) If the infusion (input) rate were changed the steady state plasma level would change but the time required to attain the steady state would be unaltered

In reality, the situation is more complex since most drugs are distributed between intravascular and extravascular compartments and thus, during the time required for the plasma levels to attain a steady value, both distribution and 'true' elimination influence the rate at which plasma level changes as well as its final steady state value This is discussed in the following paragraph Nevertheless it is clear that any change in the rate constant for elimination will have a predictable effect on the plasma level regardless of the route or method of administration For example since some antiarrhythmic drugs are eliminated by glomerular filtration, a decrease in glomerular filtration rate will (1) slow the rate of change of blood level and (2) increase the mean blood level Also since these agents may exist in tubular urine either in the charged or uncharged form, changes in urinary pH will have appreciable effects on the rate of drug reabsorption from the tubules and thus on the $t_{½}$ for excretion and plasma level

Some additional consideration of the distribution of drug within the body is essential The simplest example is the case in which the drug is administered fairly rapidly by intravenous injection When this is done the initial value of the plasma level depends on the amount injected and the blood volume The time course of the change in plasma level initially is determined by the rate at which the drug moves out of the vascular compartment When distribution is complete i e all body compartments are in equilibrium once again the rate of change of plasma level depends on the $t_{½}$ for elimination

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tion will influence both the rate of change of plasma level and the peak level If elimination is more rapid the plasma level will peak sooner after administration of a given dose and the highest value attained will be reduced in addition with more rapid elimination the plasma level will fall to a lower value before the next dose These considerations emphasize the importance of evaluating the $t_{½}$ for absorption and elimination in relation to the dose and dosing interval Failure to do so may result in selection of a dose and dosing interval that periodically create either a toxic or ineffective plasma level, or both

There are other practical advantages to knowing something about the rate constant of half times for absorption and elimination when drugs follow first order kinetics For example regardless of the dose and dosing interval the time required to attain the mean steady state plasma level is approximately 3 5 times the $t_{½}$ for elimination This provides a means of estimating the time required to attain a blood level higher than the MEC A priming dose can be used to bring the plasma level into this range more rapidly as can a shorter than normal dosing interval for the first few doses

It must be remembered however that the ability to make a semiquantitative estimate of the time course of the blood level is limited by the predictability of absorption This depends on the pH of the gastric and intestinal contents the presence of food and substances that directly or indirectly interfere with absorption and the level of motility Absorption rate also is influenced by the rate at which the drug dissolves after ingestion this can be controlled to some extent by pharmaceutical formulations

All in all while it usually is impossible to predict precisely what the time course of blood level will be for any particular patient an appreciation of the rules governing the absorption and elimination of drugs greatly increases the likelihood that any possible therapeutic effects will be attained and overt toxicity avoided

Summary

Studies on the electrophysiologic mechanisms responsible for disturbances of cardiac rate, rhythm and conduction and studies on the actions and mechanisms of action of antiarrhythmic and other drugs permit the development of an apparently reasonable approach to treatment of cardiac arrhythmias Some of the rules derived from an appreciation of cardiac electrophysiology are generally applicable Others appear to require further testing There are many discrepancies between what can be predicted or expected and what happens these discrepancies result from many factors It is likely that cardiac disease in humans has effects on the electrical activity of cardiac cells which have not been reproduced in the laboratory It is likely also that disease modifies the response of cardiac cells to drugs in ways that have not yet been discovered. Nevertheless some progress has been made and further experiment and thought may provide both better understanding and new and better therapeutic agents

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genital abnormalities at birth. Cord sera of sixteen (89 per cent) of these contained rubella specific IgM and at three months of age one of the remaining two also gave a positive result. Thus in only one of these infants rubella specific IgM antibody was not demonstrable. Twenty five of the remaining infants showed no obvious clinical abnormalities and no rubella specific IgM was found either in cord or in follow up sera. In the other 14 infants rubella specific IgM was detected but no immediate clinical abnormalities were observed. Follow up clinical studies on this group are continuing at present.

Although the importance of the detection of rubella specific IgM antibody for the diagnosis of congenital rubella infection is increasingly being recognized, few well controlled studies have been made to define the variables particularly the duration and level of the IgM antibody response and its relationship to the excretion of virus by the affected infants. We feel that more extensive studies are warranted in this direction.

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Complications of coronary arteriography

The report of de la Torre and associates[1] on embolic coronary artery occlusion in percutaneous transfemoral coronary arteriography again focuses attention on this serious complication. Unfortunately publication lag appears to account for the omission of much relevant information, and one is left with the impression that the authors are severely restricting their use of the transfemoral technique because of unavoidable and serious complications. A stand as forceful as this casts a significant shadow on an extremely useful procedure one which appears to be rapidly replacing the original Sones technique. It would seem logical, then, to summarize present thinking and practice.

There can be no doubt that acute coronary occlusion is a serious though rare complication of coronary arteriography[2,3] and that it is more common with the transfemoral than with the brachial technique. In all but one of Takaro's 33 reported complications, the transfemoral approach was utilized. Yet the increased incidence with the Judkins technique may be more apparent than real: it is the experience of all groups that complications lessen with experience and the vastly increased utilization of the Judkins technique in recent years is well known. Of critical interest then are two questions: What factors tend to create catheter thrombi and what can be done to prevent the catastrophic occurrence of embolism? The data of Nachnani and co-workers[4] suggest the role of surface artifact in the polyurethane and polyethylene catheters themselves. de la Torre and others have drawn attention to the purely physical factors favoring thrombogenesis particularly the guidewire which is not a part of the Sones procedure. We have outlined seven "caveats" of a mechanical nature which seemed important in preserving maximum "cleanliness."[4] But most surely an admonition of Judkins[5] to drastically limit the duration in which the catheter remains in the coronary vessel deserves first consideration. We have seen several instances in which the left coronary vessel has been inadvertently entered by the catheter for several minutes and its position recognized only after the onset of significant anginal pain.

We agree with Walker[6] and with Palmisano[7] that routine heparinization is valuable in the prevention of thrombotic

Annotations

Rubella-specific IgM antibody as an aid to the diagnosis of acquired and congenital rubella*

In 1941 Gregg observed after a severe rubella epidemic in 1940 an unusually high incidence of congenital cataracts in infants from Sydney and other widely separated areas of Australia[1] He wrote that the first striking factor is that the cataracts usually bilateral were obvious from birth as dense white opacities completely occupying the pupillary area Most of the babies were of small size ill nourished and difficult to feed many of them were found to be suffering from a congenital heart defect [1] In addition to the initial defects observed many other new types of malformations, either self limiting or progressive and permanent have since been recognized as part of the congenital rubella syndrome The considerable amount of knowledge acquired in recent years has resulted from careful clinical studies frequently in association with new techniques developed for the isolation of rubella virus and for the serological diagnosis of rubella infection These laboratory techniques have added importance in rubella because of the high proportion of subclinical infection to clinically apparent illness either of which may damage the fetus during pregnancy

The method of choice for the diagnosis of acquired rubella infection is of course the demonstration of a significant rise in antibody titer in paired sera collected 7 to 14 days apart and tested in parallel The method fails when an individual seeks medical advice with a retrospective history of rubella like illness occurring a week or more before or of rubella contact more than three weeks previously If the infection is in fact rubella the antibody level will in all probability have reached a peak titer and further significant increase may not be possible to demonstrate In such a situation the detection of rubella specific IgM in the serum samples would aid in the diagnosis as the IgM antibody appears initially due to the primary antigenic stimulus of rubella infection and persists for 5 to 6 weeks thereafter gradually diminishing in titer Separation and detection of rubella specific IgM may be achieved by fractionation on a sucrose density gradient [2-4] by an immunofluorescence technique [5] as well as by gel filtration on Sephadex G 200[6] or Agarose columns [7] The sucrose density fractionation although quite reliable requires the use of an ultracentrifuge an instrument not always available in many laboratories engaged in routine diagnostic virology The immunofluorescence test is the one most readily applicable for the testing of a large number of specimens but is dependent on absolute purity and specificity of reagents for reliable results For routine use especially in a non specialized laboratory Sephadex G 200 fractionation of serum coupled with rubella hemagglutination inhibiting (HI) antibody testing of the fractions thus obtained was found to be a useful and reliable technique for the detection of rubella specific IgM In our experience of testing many sera from naturally infected[6] and vaccinated persons[8] we have always been able to demonstrate specific IgM antibody in serum samples collected at proper time intervals after either primary infection or successful vaccination It may be emphasized, however that the IgM antibody generally drops to a low level after about 5 to 6 weeks following the primary infection and may then be undetectable by any of the techniques mentioned above More sensitive techniques based on radioimmunoassay or on the use of immunoabsorbent may be developed in the future to further aid the retrospective diagnosis of rubella infection

A complicating factor in the epidemiology of rubella has been the recent reports[9,10] of rubella reinfection mostly subclinical and identified by boosts in antibody titers in persons with low level immunity In reinfection during pregnancy the fetus would be harmed if only maternal viremia occurred and it is postulated that viremia would be accompanied by the presence of rubella specific IgM antibody in the blood No cases of reinfection with demonstration of rubella specific IgM have been reported until now In fact, Boué and colleagues had demonstrated[11] by serum fractionation the presence of only IgG antibody characteristic of a secondary response in three cases of reinfection during pregnancy All three patients gave birth to clinically normal infants But it is still possible that the IgM antibody if produced in reinfection may be of such low level as to be undetectable by the currently available techniques In such a situation again more sensitive methods for detection of rubella specific IgM would possibly be necessary

Because IgM globulin does not cross the intact human placenta the demonstration of circulating IgM antibody in umbilical cord or neonatal blood has proved a useful aid to the diagnosis of congenital infections due to toxoplasmosis, syphilis cytomegalovirus and rubella Of those organisms which have adverse effect on the fetus rubella has been more intensively studied and the presence of rubella specific IgM antibody is now accepted as indicative of intrauterine infection [12,13] although the absence of this antibody does not preclude it Our experience in this area has been limited largely to sucrose density centrifugation as it requires a smaller volume of serum than the Sephadex G 200 fractionation procedure Using this technique a rapid diagnosis of congenital rubella may be established as results can be available within 24 hours of birth Virus isolation may take two or three weeks and is not always successful particularly if specimens have to be transported long distances to specialized virus laboratories Congenital rubella can of course be confirmed or excluded by persistence of or fall in antibody titers but this method requires repeated testing for about six months after birth before a diagnosis can be made with certainty

In a recent study (unpublished) of 57 infants born to mothers with serologically confirmed rubella infection or with rubella like illness during pregnancy 18 showed con

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punctures in the common femoral artery and three of these were found to have intimal flaps which were excised at operation.

It was concluded that hypertension does not contribute appreciably to hemorrhage from arterial punctures and that the soft walled artery of a cardiac invalid is more likely to tear from the manipulation of a catheter and bleed than a tough atherosclerotic vessel It also seemed that puncture above the inguinal ligament tended to cause complications Because the external iliac artery slopes sharply backward, punctures in it cannot be controlled by gentle pressure so extreme pressure is often brought to bear occluding the artery and causing thrombosis This is most likely to occur in the patient who has a poor cardiac output and often has small soft arteries which are easily compressed The prognosis in these patients is good compared with the atherosclerotic patient who may have distal thrombosis In the latter occlusion is usually caused by intimal flaps or atheromatous emboli bringing to a standstill the already sluggish distal blood flow Complications after femoral puncture are not however commonly encountered in patients with atherosclerosis which supports the view that compressibility of the artery is the main predisposing factor

Operation is almost always needed in patients with arterial occlusion for although they may be symptomless when at rest in bed they will claudicate when their heart operations have been performed and they have left the hospital

There are two operative details which are very important. First if flow is poor after proximal thrombectomy the iliac artery should be rebored to produce good flow for experience has shown that unless this is done thrombosis may recur Second, after distal thrombectomy operative arteriography should be carried out for brisk retrograde bleeding can occur from collateral vessels although the main arterial trunk is still incompletely cleared.[5, 6]

It was concluded that most of the complications of femoral artery puncture can be avoided by (1) avoiding arterial catheterization in patients with polycythemia (2) puncturing the common femoral artery not the external iliac artery and (3) not using prolonged or excessive pressure to arrest hemorrhage particularly in patients with small soft arteries and a low cardiac output If the pulse disappears it is recommended that the patient be immediately heparinized and an emergency operation carried out even in the absence of symptoms

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The trabeculae carneae—A thought

The function of the trabeculae carneae is not well understood. Surely they are not just ornaments. Nevertheless even though their function is not fully established, it is quite likely that their mere presence and the irregular internal surface which they produce in the ventricles serve in part to assist in overcoming the kinetic energy of the blood flowing into the ventricles during diastole The slowing of inflowing blood by the trabeculae carneae reduces the kinetic energy which would otherwise have to be overcome by the myocardium as systole begins and ejection starts Thus, the irregular internal surface of the ventricle tends to make the inflowing blood approach a state of standstill so that the contractile force of the myocardium is utilized mainly to set the blood into motion and is not imposed upon to any great extent merely to bring the inflowing blood to a halt before the direction of flow can be reversed to allow the blood to enter the pulmonary artery and aorta

With this concept in mind, it would be expected that the internal surface of the thin walled right ventricle would be especially irregular or rough since so much blood gushes into it as occurs when an individual lies down and pooled blood pours into the ventricle from the lower parts of the body Thus the right ventricle could profit energywise or mechanically by having a rougher interior than the left ventricle And, of course the interior of the thin walled right ventricle actually has an extremely irregular internal surface making it possible to slow the blood flowing into the thin walled and relatively weak ventricle which cannot waste contractile force merely in overcoming the kinetic energy of the inflowing blood.

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complications with transfemoral coronary angiography Perhaps motivated by the same reasoning as they (the desire to avoid such ominous complications and the simplicity of the method) we have routinely injected 5 000 units of aqueous heparin immediately prior to coronary arteriography Along with Walker [6] we have noted no thrombotic problems whatever in approximately 200 catheterizations during the past two years Though Chaitman and co workers[8] are unconvinced that heparinization is the critical factor it would seem logical to continue this potentially preventive procedure until more precise evidence is available Finally since it is still not entirely clear whether patient choice training or heparin prophylaxis represents the critical factor our attention should not remain fixed upon any one of these facets exclusively

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The dangers of femoral artery puncture and catheterization

Catheterization or needle puncture of the femoral artery may cause hemorrhage or occlusion and it is agreed that in these circumstances early operation is needed for delay may result in loss of the limb [1 4]

Thirty six cases of complications following femoral artery punctures were reviewed Eleven cases bled sufficiently for a surgical opinion to be sought and two of these were hypertensive Nine cases responded to conservative measures and only two needed operation One of these was hypertensive and the hematoma was found to originate from a puncture in the common femoral artery The other case was normotensive and the arterial puncture was above the inguinal ligament

Eleven males and fourteen females had arterial occlusions but only eight of the 25 had early symptoms Eleven of the fourteen females had heart disease the other three having polycythemia Raynaud s phenomenon and atherosclerosis respectively Of the men four had heart disease four atherosclerosis two had both and one had polycythemia In at least three of the women occlusion occurred after prolonged pressure had been applied in an attempt to arrest bleeding Only seven patients were treated within six hours of arterial occlusion the delay often being due to an initial diagnosis of arterial spasm

Distal thrombosis was found to carry a poor prognosis and except in one case where the superficial femoral artery was punctured and thrombosed distally it occurred only in the presence of polycythemia (one case) or severe atheroma (five cases)

Twenty one cases of arterial occlusion were operated on Two of these had severe atheroma and distal thrombosis and the limbs were amputated after unsuccessful attempts to restore the circulation A third patient with distal thrombosis had polycythemia and died after an unsuccessful operation Of the remaining eighteen operated cases three all with severe atherosclerosis, had distal thrombosi One was due to an atheromatous plaque which had been dislodged from the site of the femoral artery puncture and occluded the popliteal artery thrombectomy with a Fogarty catheter was successful In the second patient with distal thrombosis a common femoral artery rebore and distal thrombectomy were successful The third patient with distal thrombosis and atherosclerosis was treated by thrombectomy alone which resulted in rethrombosis and claudication the iliac artery was severely diseased and perhaps should have been rebored to achieve a successful result The remainder had proximal thrombosis only and were successfully treated by thrombectomy the common femoral artery being closed with a vein patch

A least seven punctures were above the inguinal ligament and all these had proximal thrombosis only Six had

Prinzmetal's variant angina

To the Editor

In a recent study on Prinzmetal's variant angina (Am Heart J 87 304 1974) which we greatly appreciated, Drs Bodenheimer Lipski Donoso and Dack reported a case of an atrioventricular (A V) block observed in a patient in whom the variant angina affected the inferior wall of the heart. Since a similar finding is also present in all other cases of variant angina complicated by an A V block that we have found in the literature[1-7] we would like to know from the authors if it is right to maintain that variant angina can be complicated by an A V block only if the angina develops in the inferior wall of the heart

Considering also that in A V blocks complicating a variant angina the QRS complex is always[1-8] of supraventricular type would it be possible to argue that a *transitory* disturbance of blood supply can cause an A V block only in the first portion of the conducting system while this is not possible in the distal portion?

The multiple vascularization of the distal portion of the conducting system provided both from the left and the right coronary arteries and its high resistance to ischemia[9] do therefore allow us to maintain that in coronary heart disease a disturbance of blood supply never does cause an A V block in the distal portion of the conducting system without a concomitant myocardial infarction

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Reply

To the Editor

We thank Dr Fazzini and Dr Marchi for their comments concerning atrioventricular block in variant angina

Of central importance is probably that the AV node receives a single blood supply either the right coronary artery in 85 per cent or the left circumflex in the remainder[1] Since the active coronary lesion in variant angina seems to involve one vessel the AV node with its single supply would be frequently involved The inferior wall which also receives its supply from the right coronary artery and/or the left circumflex coronary artery would at times be associated with AV block On the other hand, the His bundle and the proximal right and left bundle branches receive a dual blood supply involving both the right and left coronary arteries[1] Thus active lesions in two coronary arteries would be required to cause AV block at this level Recently Betriu and coworkers[2] have described a patient with lesions in both the dominant right coronary artery and the left anterior descending artery with variant changes in the anterior precordial leads. This patient demonstrated AV block during his attacks of chest pain. Furthermore despite recurrent episodes of AV block and changes in the anterior precordial leads no evidence of an acute myocardial infarction appeared. This case documents that AV block can occur in patients with anterior wall ischemia Its relative rarity is probably related to the dual blood supply in this area and the fact that variant angina is generally associated with active disease of a single coronary artery

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Complications of cardiac resuscitation

To the Editor

We recently came upon two *extraordinary* complications of closed chest cardiac resuscitation[1] That experience prompted us to construct the accompanying table as a reference bank *on resuscitative* mishaps Practitioners should know about the ill effects of resuscitation because such knowledge will help them render more enlightened care during and after the procedure

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Letters to the Editor

Experimental response curves

To the Editor

We read with interest the article by Bonney and Rustan entitled Experimental response curves A means of predicting pacemaker response to electrical interference (Am Heart J 87 757 1974) From the results of bench testing and in vivo testing of the same pacemakers the authors conclude that their in vivo test method represents the worst case condition Although this conclusion seems reasonable for the frequencies of the electromagnetic radiation used (10 5 19 3 and 26 6 MHz) it cannot be extended to higher frequencies

Interfering radiation can enter a pacemaker directly and via the electrode acting as an antenna Metal shielding prevents the direct entry The function of an antenna is optimal when it measures one fourth of the wave length or an uneven multiple of it In the microwave region where electrode length and wave length are of the same magnitude changes in electrode length result in marked variations of the pacemaker threshold[1] Similar variations of the pacemaker threshold occur with changes in the orientation of the pace maker electrode system[1] After implantation neither electrode length nor pacemaker and electrode orientation can be assessed accurately or be varied From the data presented by Bonney and Rustan tissue shielding appeared to be of minor importance It was found to be a significant factor by Schlentz[2] Table I summarizes the results of our comparative pacemaker susceptibility tests in air fat water and saline in an electromagnetic field with a frequency of 1 3 GHz = 23 cm wave length[1] In air the susceptibility of both pacemaker groups was determined by radiation received through the electrode In these media the unshielded pacemakers were disturbed by direct circuit interference whereas the metal shielded units could only pick up the interfering signals via the electrode The attenuation ratio for the unshielded pacemakers was the result of the attenuation afforded to the penetrating wave by the media The attenuation ratio for the metal shielded units however was due to attenuation and decreased resonance capability of the electrode in these media

The data indicate that fat provides the least shielding Therefore only tests in fat include the worst case condition

Table I Attenuation ratio (shielding factor)* of a 1 cm layer of three media for two groups of non competitive pacemakers tested in an electromagnetic field with a frequency of 1 3 GHz

	Fat	*Tap water*	*0 9 per cent NaCl solution*
Unshielded pacemakers	1 2	3 3	7 3
Metal shielded pacemakers	2 1	15	113

The attenuation ratio is the quotient of the threshold level (in volts/meter) determined from the tests in these media divided by the threshold levels determined from tests in air From Röhl Laun Hauber Voigt and Stauch Biomed Tech 18 209 1973 Reproduced with permission

after implantation. Testing in fat is difficult Because the results obtained in fat are similar to those in air we recommend that testing of pacemaker susceptibility to HF electromagnetic radiation should be done in air with an electrode length of one fourth of the wave length and with pacemaker and electrode in their most sensitive orientation.

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Reply

To the Editor

We thank Dr Röhl for his interest in the pacemaker data which we published (Am Heart J 87 757 1974) and for calling to our attention his work in this area To carry the data beyond the 10 5 to 26 6 MHz bandwidth reported in the article would be inappropriate and should only be done on the basis of additional data

How best to test a pacemaker is a subject discussed in many circles A bench test approach certainly seems to give an indication of a unit s susceptibility to interference However we have felt that the animal model offers a good preparation for simulating the clinical use of pacemakers As Dr Rohl has noted the difference between the two may not seem great but such differences become apparent only when a comparison of the two testing methodologies is carried out (Often dogmatic advocates of bench testing without biological tests do not have the facilities to prepare animal models) Additionally when attempting to simulate and evaluate the clinical situation through the animal model we felt that we were less likely to become engrossed in a testing for testing s sake endeavor Should a bench test with the electrodes carefully positioned to act as an optimal one fourth wave length antenna be conducted at some future point this data in itself would be difficult to relate to a clinical framework unless accompanied by either reference to clinical data or companion data based on an animal model

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Table I Complications of closed chest cardiac resuscitation*

Cardiac

MYOCARDIUM
- Rupture
  - Atrium[2†]
  - Ventricle
    - Through infarcted tissue[3]
    - Through normal tissue[4]
- Perforation (ventricle)
  - By fractured rib[4]
  - By dorsal osteophyte[1]
- Hematoma[5]
- Hemorrhage[6] (subendo and subepicardial)

PERICARDIUM
- Hemorrhage
  - With tamponade[3,7]
  - Without tamponade[8,14]
- Inflammation[15]
- Laceration[4]
- Rupture[4]
- Ecchymosis[16]

ASSOCIATED WITH MITRAL PROSTHESES
- *Disruption*[17] *(of prosthesis)*
- Rupture[18] (coronary artery)
- Laceration[19] (A V groove)
- Hematoma[19] (biventricular and septal)

OTHER
- Papillary muscle rupture[20]
- *Intra atrial thrombosis*[8,21]

Gastrointestinal

RUPTURE
- Esophagus[22]
- Diaphragm[23]
- Stomach[23,26]
- Colon[27]

LACERATION
- Esophagogastric mucosa[23,25,28]
  - With hematemesis[28]
- Liver[6,8,9,14,15,23,25,29,30]
- Spleen[6,14,25,29]

PANCREAS
- Hemorrhage[16,29]
- Inflammation[16]

OTHER
- Torn hepatic falciform ligament[29]
- Chylous ascites?[31]

Skeletal

FRACTURE
- Rib[2,5,6,8,15,17,20,23,25,28,31]
- Sternum[6,9,11,13,15,25,28,30]
- Scapula[11]

OTHER
- Separated costochondral junction[12,30]
- Flail chest[11,30]

Respiratory

PLEURA
- Hemothorax[2,4,6,9,12,14,29]
- Pneumothorax
  - Tension[25,29]
  - Non tension[11,12,14,15,17,22,25,29]

LUNG
- Hemorrhage[14,16,25,29]
- Laceration[9]

OTHER
- Tracheal laceration[25]
- Aspiration[12]
- Pneumomediastinum[25]

Vascular

RUPTURE
- Ascending aorta[13,32]
- Inferior vena cava[9,14]
- Splenic vein[29]
- Internal mammary vein[29]

OTHER
- *Dissecting aneurysm*[33] *(ascending aorta)*
- Hemorrhage around portal vein[25]
- Intravascular coagulation?[34]

Embolic

BONE MARROW
- To lung[2,6,8,10,12,14,20,21,31,34]
- *To right atrium*[2,8,21]

FAT
- *To lung*[10,12,35]
- To kidney[10]
- To cerebrum[35]
- To ocular vessels[36]

ATHEROMATOUS
- To kidney adrenal spleen brain[37]

LUNG TISSUE
- To cerebellum[38]

MURAL THROMBUS
- To superior mesenteric artery[39]

Miscellaneous

NEUROPSYCHIATRIC[30,40,42]

CHEST WALL TRAUMA[23,31]

SUBCUTANEOUS EMPHYSEMA[11,14,25,43]

ADRENAL HEMORRHAGE[14]

RETROPERITONEAL HEMORRHAGE[16,25,29]

HEMOGLOBINURIA[44]

HYPEROSMOLALITY[45]

SCROTAL PNEUMATOCELE[43]

PNEUMOPERITONEUM
- With ruptured viscus[22,24,26]
- *Idiopathic*[1,43]

*Arranged without regard to frequency or importance

†References are representative but not all inclusive

Books received

All About High Blood Pressure By Ivan A D Cruz, M D M R C P New Delhi 1974 Orient Longman, Ltd. 199 pages.

Angina Pectoris Edited by Oglesby Paul M D New York, 1974 Medcom Press 135 pages

Emergency Care Assessment and Intervention Edited by Carmen Warner Sproul R.N P H.N and Patrick J Mullanney M D St. Louis 1974 The C V Mosby Company 374 pages. Price $12 50

Medical Care and Rehabilitation of the Aged and Chronically Ill By Charles D Bonner M D Boston, 1974 Little Brown & Company 297 pages Price $16 50

Review of Medical Pharmacology ed 4 By Frederick H Meyers, M D Ernest Jawetz, Ph D and Alan Goldfien M D *Los Altos Calif 1974 Lange Medical Publications, 692* pages

Biochemical and Clinical Aspects of Peptide and Amino Acid Absorption Edited by K Rommell and H Goebell Conference on Biochemical and Clinical Aspects of Peptide and Amino Acid Absorption, October 1972 Black Forest Germany Stuttgart 1974 F K Schattauer Verlag, 116 pages.

Book reviews

Biomedical science and cardiovascular dynamics Edited by Gojmir Južnič Assistant Editors C Ambrosi Marseille D C Deuchar London A Falcão De Freitas Oporto A A Knoop Amsterdam and P D Verdouw Rotterdam Basel Munchen Paris London New York Sydney 1973 S Karger AG 318 pp

This volume No 31 of Bibliotheca Cardiologica on Biomedical Science and Cardiovascular Dynamics, Part II is a companion publication to Part I of the same subject The contributions to this edition describe studies related to physics physiology pharmacology and clinical practical aspects of hemodynamic phenomena In view of the tremendous surge of activity in cardiac catheterization in man this publication should be of considerable interest to all people interested in cardiology both experimental and clinical. Those who follow the medical literature closely will find relatively little new in this book Nevertheless the many papers included provide an accurate summary of the concepts of hemodynamic phenomena as they are considered at the present time The respective papers are short but succinct. This is another useful and valuable publication

Microcirculation Edited by Mary P Wiedeman Ph D Philadelphia 1974 Dowden Hutchinson and Ross Inc 421 pp $22 00

This is an interesting book on the history of microcirculation The section on the early history of investigators and investigation in microcirculation are particularly valuable aspects of this book Dr Mary Wiedeman has ably reviewed the important early studies of William Harvey August Krogh the Clarks Knisely Folkow and others Those who have been actively engaged in microvascular research and especially those who worked in the field while Krogh still lived will appreciate the book most Although it is not possible to summarize with justice all the important work already published in the field in about 400 pages Dr Wiedeman has done a fine job in the phases and about the investigators selected for her book She is Secretary Treasurer of the Microcirculatory Society

Advances in cardiology Vol II A perspective on new techniques in congenital and acquired heart disease Edited by John H K Vogel Basel 1974 S Karger AG 215 pp $33 80

This eleventh volume on Advances in Cardiology devoted to new techniques in the management of heart disease devotes a major portion to surgical aspects of the management of congenital defects pulmonary hypertension, coronary heart disease and valve replacement Such subjects as balloon atrioseptostomy correction of complete truncus arteriosus genetic counseling of congenital heart disease pathology of Eisenmenger syndrome and natural and unnatural history of acute coronary artery disease are reviewed. The series of Advances in Cardiology are valuable contributions to cardiology and this volume is another good addition. It is worth owning each volume

Advances in cardiology Vol 10—Body surface mapping of cardiac fields Edited by Stanley Rush and Eugene Lepeschkin, Basel Switzerland 1974 S Karger A G 331 pp Price $44 05

This issue of *Advances in Cardiology* is highly technical and will interest only laboratory investigators The brief historical presentation by Frank Wilson s daughter is particularly interesting to cardiologists who knew her father Certainly those who are involved in a study of surfacing mapping of cardiac fields will study this book Applications of this type of analysis in clinical medicine shall be limited because of its complexity With greater use of computers mapping may be made a practical procedure The experimental applications are important however

Mechanisms of Hypertension. Edited by Mohinder P Sambhi M D Ph.D New York, 1973 Excerpta Medica Foundation, 389 pages

This publication on the mechanisms of hypertension represents the proceedings of a conference held in Los Angeles during March 1973 Hypertension is the disease presently in vogue Therefore those interested in the mechanisms by which arterial hypertension develop will find the papers of this publication of interest. Among the subjects discussed are regulatory mechanisms of essential hypertension and renal hypertension, the role of the adrenal hormones humoral factors in the production of hypertension with greatest emphasis on renin risk factors and management of the hypertension This is a good review of the subject with the contributors being those who are actively engaged in their respective interests The book should interest all physiologists and clinicians

Books received

All About High Blood Pressure By Ivan A D Cruz, M D M R C P New Delhi, 1974 Orient Longman, Ltd. 199 pages.

Angina Pectoris Edited by Oglesby Paul M D New York, 1974 Medcom Press, 135 pages.

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Biochemical and Clinical Aspects of Peptide and Amino Acid Absorption Edited by K Rommell and H Goebell Conference on Biochemical and Clinical Aspects of Peptide and Amino Acid Absorption October 1972 Black Forest Germany Stuttgart 1974 F K. Schattauer Verlag 116 pages.

Lucien Dautrebande Foundation Triennial Prize

In the presence of H R M Princess Paola of Belgium the Fondation de Physiopathologie Professeur Lucien Dautrebande awarded its triennial prize to Professor Dirk Durrer, Amsterdam for his remarkable contribution concerning clinical and electrophysiological knowledge of the heart

The next prize approximately 500 000 Belgian francs will be awarded during the year 1976 The award will be made for a work dealing with human and animal physiopathology preferably having therapeutic implications For further information regarding this competition please write Office of the Foundation of Physiopathologie Professeur Lucien Dautrebande 35 chaussée de Liége 5200 HUY Belgium

Application of nutrition in the health sciences

The University of Texas Health Science Center at Houston Division of Continuing Education and the Texas Medical Center Inc announce The third annual Texas Medical Center Symposium on the Application of Nutrition in the Health Sciences to be held in Houston Texas on February 7 and 8 1975 The theme of this program will be The role of nutrition in the clinical management of the patient The program will be constructed around heart disease cancer obesity and the nutritional management of the in patient as well as the out patient For further information write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Postgraduate medical seminar cruise

The Department of Postgraduate Medicine of Albany Medical College announces the sixteenth annual Postgraduate Medical Seminar Cruise from February 15 through February 28 1975 The 13 day cruise aboard the Italian liner S S Michaelangelo will include visits to Montego Bay San Juan Barbados St Vincent Antigua and St Thomas

The faculty of the Albany Medical College will present a program of particular interest to general internists and family practice physicians. Topics include Underlying Pathology in Cardiac Disease Clinical Cardiology Delivery of Psychiatric Care at the Community Level Innovative Health Care Delivery System End Stage Renal Disease and the Diagnosis of Surgically Correctable Causes of Urinary Tract Infection Albany Medical College of Union University is accredited by the Council on Medical Education of the American Medical Association to offer courses in continuing medical education Registration at such courses is acceptable for credit toward the American Medical Association s Physician s Recognition Award. The Postgraduate Medical Seminar Cruise is approved for 22 hours of continuing education credit Request has been made to the Commission on Education American Academy of Family Physicians for approval of the program for prescribed education credit

For further information write to Frank M Woolsey Jr M D Department of Postgraduate Medicine Albany Medical College Albany N Y 12208

American Board of Internal Medicine examination

The examination of the American Board of Internal Medicine in the subspecialty area of Cardiovascular Disease will be administered on Tuesday October 21 1975 Registration begins January 1 1975 and ends March 15 1975 For information and application forms please write American Board of Internal Medicine 3930 Chestnut St Philadelphia Pa 19104

American Heart Journal

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Editorial

? IHSS ? HOCM ? ASH a plea for unity

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London, England

As is usually the case terminology proliferates when ignorance abounds and the multiple titles given to the same condition bear eloquent witness to the large gaps in our knowledge There can be little doubt that idiopathic hypertrophic subaortic stenosis (IHSS) in the United States and hypertrophic obstructive cardiomyopathy (HOCM) in Europe are one and the same disease The term IHSS has rightly led to the disorder being classified with other forms of left ventricular outflow tract obstruction but has tended, unfortunately to exclude it from the family of cardiomyopathies and to obscure some features of the disease

The naked eye appearances of the heart so well described by Teare in 1958[1] have been demonstrated on innumerable occasions and the disordered hemodynamics with obstructive pressure gradients across the left ventricular outflow tract in roughly 80 per cent of patients at some time during the course of the disease have been extensively studied. Recently more attention has been paid to what may be termed the diastolic component of the condition and it has been shown that an increase in left ventricular end diastolic pressure and a decrease in end systolic volume are both features of the condition Left ventricular filling is slower than normal[2] and the reduction in volume and increase in pressure suggest reduced distensibility or compliance of the left ventricle Studies with both beta adrenergic stimulating and blocking drugs have shown a decrease in distensibility with beta adrenergic stimulation and an increase with beta adrenergic blockade For example isoprenalin produces an increase in end diastolic pressure which is not due to the effect of tachycardia since pacing the ventricle at the same rate causes a fall in diastolic pressure Beta adrenergic blockade however produces an increase in volume and a decrease in pressure indicating an improvement in distensibility[3]

The microscopic appearances are now well documented, the abnormal muscle fibers being short thick fragmented and interspersed with fibrous tissue They have large nuclei with a wide perinuclear space and are arranged in circular formations or whorls These characteristic muscle fibers may be found in collections throughout the myocardium often with a concentration in the septum producing the characteristic septal bulge The demonstration by Ferrans Morrow and Roberts[4] of abnormal branching of myofilaments and abnormal attachment of Z-bands with cells running in abnormal directions instead of parallel is of crucial importance These workers have found that these myofibrils were often oriented obliquely or perpendicular to the longitudinal axis of the cells and that some myofibrils originate from a single Z-band inserted into other

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Z bands It seems likely that these abnormalities are the basic and specific hallmark of hypertrophic obstructive cardiomyopathy (or *idiopathic hypertrophic subaortic stenosis*) and that they may account for the abnormalities of function Ferrans Morrow, and Roberts[4] suggest that the divergence of the planes of orientation of the individual cells would result in some cells undergoing shortening while other cells may be held isometrically or even be in actual stretch Such a *situation could constitute* a *powerful* stimulus to hypertrophy and could also induce *abnormal patterns of contractility and perhaps* impair relaxation thus explaining both the outflow tract and filling abnormalities in the disease The similarity between the appearance in *HOCM* (IHSS) and the branching myofibrils found in the primitive heart such as in crustaceans or the salamander suggest the possibility that the abnormally orientated fibers are the result of a disorder of the growing myocardium Manasek[5] has shown the importance of regular alignment of *myofibrils in the developing cardiac loop and has* pointed out that myofibrillar alignment eventually coincides with the linear forces of contraction within a cell It is possible that with cardiac muscle as with other structures mechanical *forces determine the patterns of orientation* However Ferrans Morrow and Roberts consider that the oblique or transverse arrangement of the myofibrils in HOCM (IHSS) probably results from abnormal mechanical forces related to the *abnormal angles of pull exerted on individual* cells by abnormally orientated neighboring cells

A genetic basis for HOCM is undoubted and there is little evidence for the suggestion that two types of disease exist, one on a familial and the other on a nonfamilial basis *The disease varies* enormously in its extent and speed of progression and it is likely that minor degrees may not be detectable clinically so that the familial incidence is obscured in many patients The behavior of the disease and *its manifestations are virtually* identical both in familial and so called nonfamilial patients so that it is scarcely convincing to suggest two separate groups with a different genetic basis It has been suggested that the earliest *manifestations of* the disease may lie in disproportionate hypertrophy of the septum and that this may be detectable by echocardiography[6] before clinical manifestations are obvious If this proves to be the case in large numbers of patients, an important step forward has been taken in the early detection and monitoring of the progress of the disease The abnormally large septum, which is found to exceed the thickness of the posterior wall of the left ventricle by a ratio of more than 1 3 1, *was not found with other forms of outflow* tract obstruction or in normal subjects The thickness of the septum has been termed "asymmetric septal hypertrophy" or ASH and it has been further suggested that this may be a more *appropriate term for the disease than IHSS* or HOCM, particularly when outflow tract obstruction is absent

The use of the term asymmetric hypertrophy induces a sense of *deja vu* for it was this term that Teare used to describe the disease in *1958*[1] and it would seem that the introduction of yet *another term for HOCM or IHSS* is unwarranted and may make confusion worse

Although much has been learned about HOCM in the last ten years much more still remains to be learned and it is these crucial areas of ig*norance that should stimulate the greatest* interest and endeavor

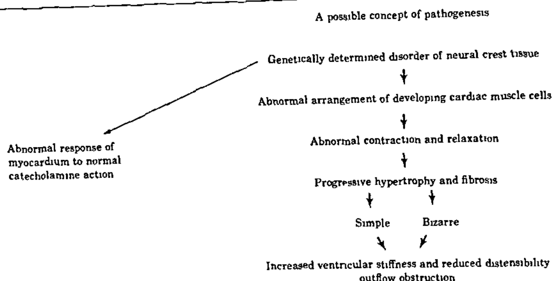
The outstanding features that are as yet ill understood or largely unknown are those concerning the cause of the disease the possible asso*ciation with abnormalities of* catecholamine function, and the association (real or imaginary) with other diseases The latter concept involves the development of a secondary" form of hypertrophic obstructive cardiomyopathy induced *by certain stimuli* particularly resistance to the outflow of the left ventricle by fixed obstruction or systemic hypertension Although much has been learned about prognosis the determinants and predictors of sudden death are still largely *unknown Finally treatment is still* a matter of controversy and often unsatisfactory

It is worthwhile therefore considering these various parameters of ignorance a little further

Regarding the cause of the disorder, the theo*ries of Ferrans, Morrow* and Roberts[4] have the most appeal and the similarity of the abnormal heart muscle cells in hypertrophic obstructive cardiomyopathy to certain primitive hearts prompts the thought that hypertrophic cardiomyopathy may represent a form of cardiac atavism

Can this theory be related in any way to abnormality of catecholamine *function* (Table I)? There are a number of factors which suggest a

Table I Hypertrophic obstructive cardiomyopathy



connection First there is the association between systemic hypertension and hypertrophic obstructive cardiomyopathy noted first by Brock in 1957[7] Second, there is the finding of noradrenosis in the left ventricular outflow tract by Pearse[8] although admittedly this has not been confirmed. Von Noorden Olsen and Pearse[9] have found that autofluorescence similar to that of noradrenaline was found in connective tissue in both HOCM and control hearts although the hearts from the former tended to fluoresce more strongly than the controls The presence of noradrenaline was not confirmed by microspectrofluorometric methods but at the time only emission spectra could be examined.

A somewhat stronger argument for the association between catecholamines and the myocardial abnormality comes from hemodynamic studies in which inotropic stimulation with isoprenalin produces an increase in left ventricular end diastolic pressure that is not due to the positive chronotropic effect. Conversely beta adrenergic blockade produces a fall in left ventricular end diastolic pressure and an increase in volume of the ventricle suggesting improvement in distensibility[3] These findings would suggest that positive catecholamine action makes the left ventricle stiffer and accentuates the functional abnormality whereas negative inotropic effects have the reverse action

Then there is the association between both pheochromocytoma and neurofibromatosis on the one hand, and lentiginosis on the other with HOCM although an excess of vanilylmandelic acid in the urine is not found in patients with hypertrophic obstructive cardiomyopathy More interesting perhaps is the association between lentiginosis and hypertrophic obstructive cardiomyopathy Polani and Moynihan[10] described a syndrome of multiple symmetrical lentigines with left sided obstructive cardiomyopathy retardation of growth and sometimes intellectual impairment They suggested that the cause of the disorder might be dysfunction of pigments and other elements of neural crest origin and they postulated that the cardiac lesion was related through a neural crest origin either primarily (for it is known that the neural crest contributes to heart structures) or secondarily related to the lentigines perhaps by a biochemical mechanism It is conceivable that all types of cells that produce adrenaline and noradrenaline have ultimately a neural crest origin

It seems possible that the abnormal arrangement of cells in the myocardium and the abnormalities of systolic and diastolic function might both be the result of excessive sympathetic action through a developmental abnormality of the neural crest through an excessive production of catecholamines, or abnormal response to catecholamines of developing heart muscle A further interesting association is the similarity

between the cardiomyopathy of Friedreich's ataxia and hypertrophic obstructive cardiomyopathy In Friedreich's ataxia there is massive myocardial hypertrophy while outflow tract obstruction to both ventricles has been well documented As in hypertrophic cardiomyopathy, this obstruction may disappear as the patient becomes older and may represent a deterioration in the disease It has been postulated that in Friedreich s ataxia, an autonomic imbalance may be responsible for some of the cardiac abnormalities A striking difference however, between HOCM and Friedreich's ataxia is the pressure of occlusive lesions of the coronary arterioles found in the latter but not in the former

There are many gaps in the chain of evidence linking HOCM with a disorder of catecholamine function Most patients with HOCM are not hypertensive nor do they have the features of physical retardation and intellectual impairment found in Polani and Moynihan s syndrome although both conditions appear to be inherited on a similar genetic basis However further studies of catecholamine output the response of the abnormal heart muscle to catecholamine stimulation and the catecholamine content of outflow tract muscle are necessary to study this postulate further

Yet another problem concerns the association of HOCM with other conditions, particularly fixed outflow tract obstruction of the left ventricle and systemic hypertension It is not known whether HOCM can be produced as a result of severe protracted outflow tract obstruction or after load or whether the presence of HOCM in such patients is the result of a chance association The rarity of HOCM in patients with fixed outflow tract obstruction (which is a common disease) strongly suggests that the association is a matter of chance It is clear that congenital heart disease although rare, does occur in association with HOCM The recent study of two patients[11] with ventricular septal defect and with evidence of HOCM in the muscle of the infundibulum in association with progressive infundibular stenosis is of extreme interest There are obviously two possible explanations for this The one that the stress imposed upon the right ventricle by the ventricular septal defect has resulted in the development of HOCM in the infundibular muscle and the other (to which the authors incline) that the abnormal cells of HOCM were already present in the infundibulum and lead to localized hypertrophy and progressive infundibular obstruction It is possible that HOCM in the outflow tract of the right ventricle in association with ventricular septal defect may be more common than is realized and such patients may be masquerading as examples of lone pulmonary stenosis or ventricular septal defect with pulmonary stenosis or the tetralogy of Fallot Other forms of congenital heart disease may help to mask HOCM, such as inter atrial communications and transposition of the great arteries, aortic valve stenosis discrete subvalvular aortic stenosis and patent ductus arteriosus

Massive hypertrophy of the heart is not confined to HOCM The report of Ehlers and coworkers[12] of massive hypertrophy of the left ventricle and septum in Pompé s disease producing a naked eye appearance of the heart indistinguishable from HOCM is now well known The histology, however is entirely different, and although there is an excess of glycogen in the heart in HOCM, the extensive vacuolation of muscle fibers due to glycogen infiltration in Pompe s disease is entirely different

While the causation and association factors in HOCM remain largely unknown, further information is accumulating regarding the natural history and the effects of treatment Studies[13] of the natural history of 120 patients with HOCM followed for an average of five years revealed that the average age of onset of symptoms was 28 years and the average duration of symptoms before death nine years Most patients deteriorated slowly, the minority (approximately 10 per cent) developing atrial fibrillation which usually produced a striking increase in symptoms As is well known sudden death can occur at any age and without warning and occurred in 19 patients in this series Young males with a family history seemed to be more prone to die suddenly than other patients The estimated mortality was 15 per cent at five years and 25 per cent at ten years giving an annual mortality of 3 5 per cent A previous study[14] of the symptomatic course of the disease suggested that the prognosis was related more to the height of the left ventricular end diastolic pressure than to the outflow tract gradient Progressive deterioration tended to be accompanied by progressive loss of outflow tract obstruction and congestive heart failure often with atrial fibrillation and sometimes with sy

stemic embolism Apparently this stage of loss of outflow tract obstruction is not necessarily ac companied by ventricular dilation although we cannot exclude this possibility In my experience however the filling difficulty appears to be ag gravated by defective contractile force due either to the progression of the disease throughout the myocardium or to the development of widespread fibrosis It is not known which of these factors is the more important or indeed whether both may occur Loss of outflow tract obstruction after the development of infarction of the ventricular wall leading to dyskinesia and deficient contractile force in that area has been noted and further supports the view that loss of outflow tract obstruction is associated with impairment of con tractile function and may indicate progression of the disease and deterioration in the prognosis

In a recent study of myocardium obtained at operation and necropsy in patients with both obstructive and nonobstructive hypertrophic car diomyopathy all the muscle specimens showed the characteristic changes in the muscle cells In those patients who had obstruction these abnor malities were either absent or only very rarely present in tissue from the left ventricular apex posterior wall, or right ventricle By contrast many abnormal cells were present both in the left ventricular free wall and the right ventricle in seven of the nine patients without obstruction who were symptomatic [15] These findings which suggest that the characteristic cellular abnor malities are always present in the septum but that more extensive involvement of the free walls of the ventricles is limited to patients with out obstruction also supports the concept that the more widespread is the disease the less in the obstruction and probably the worse in the prog nosis

A recent multicenter study[16] into the natural history of hypertrophic obstructive cardiomyopa thy concerned the course of 190 patients with proved left ventricular outflow obstruction The incidence of severe symptoms increased with each decade from 9 per cent in the first decade to 70 per cent in the sixth to eighth decade The an nual mortality was 3 5 per cent, exactly the same figure as reported from one of the participating centers [13] Excluding those patients who died following surgical treatment 31 of the remaining 172 patients died, 26 of the 31 deaths being sud den Unquestionably sudden death is the most important feature of the natural history and so far studies have not indicated a reliable means of prediction though in one study[14] there was a tendency for sudden death to be more common in those patients with a short progressive symp tomatic history and particularly high left ventricular end diastolic pressures The pattern of the disease is determined mainly by the site and extent of the specific lesions in the myocar dium but perhaps also by simple hypertrophy that is stimulated by the abnormal patterns of contraction

Against this background of causation and prognosis the effects of treatment may be ex amined

The treatment of hypertrophic cardiomyopa thy can be considered under four headings Beta adrenergic blockade surgery the management of the phase of congestive heart failure atrial fibrillation and embolism and finally prevention of sudden death and of the progression of the dis ease

Beta adrenergic blockade is the most logical form of treatment in view of what is known about the behavior of the disease The effects of beta adrenergic blockade in preventing the de velopment of outflow tract gradients after in otropic intervention or exercise and on improv ing distensibility of the left ventricle together with reduction of left ventricular end diastolic hypertension all add weight to this view In addi tion beta adrenergic blockade can relieve angi na and diminish dyspnea presumably by reduc ing cardiac work and lowering left ventricular diastolic pressure respectively Hopes for an effective treatment of hypertrophic cardi omyopathy by beta adrenergic blockade (which were initially high) have to some extent been dampened by the difficulties of assessing the progress of treatment uncertainty about optimal drug dosage and the continuing incidence of sud den death An early trial[17] of propranolol in doses of 120 mg daily showed that angina was relieved or diminished in two thirds of the patients and that this effect was more pronounced when there was appreciable outflow tract obstruction and the left ventricular end diastolic pressure was within normal at rest. These results suggested that the main symptomatic benefits might be in those pa tients in whom the disease was localized to the outflow tract giving a concentration of the spe cific lesions in the septum rather than in a more

generalized form But the study did not permit objective assessment of the effect of the drug on the hemodynamics A subsequent double blind trial using practolol propranolol, and a placebo yielded more information [18] Dosage was considerably larger than in the previous trial, being 320 mg a day of propranolol and 800 mg a day of practolol These two drugs and a placebo were each administered for four weeks to each patient in a double blind manner Dyspnea was improved but only in patients with severe symptoms angina was improved in the majority of patients and the left ventricular ejection time index was significantly prolonged with propranolol but not with practolol Both drugs reduced the A wave of the apex cardiogram and the isovolumic relaxation time The results confirmed the symptomatic benefit from beta blockade and suggested some advantage of propranolol over practolol The reduction in the size of the A wave in the apex cardiogram and the reduction in the isovolumic relaxation time were both considered to be the result of improved distensibility and reduced stiffness of the left ventricle The possibility that the reduction in the A wave might be the result of diminished atrial drive could be considered but this mechanism would not explain the reduction in isovolumic relaxation time Adelman and co workers [19] using propranolol for periods of six to 34 months, concluded that beta adrenergic blockade was likely to be more effective in those patients with latent or variable than in those with fixed, obstruction The effects of beta adrenergic blockade on the hemodynamics of HOCM during exercise have also been studied [20] The most notable effect of long term administration of propranolol was the restriction of tachycardia on effort. When practolol was used this effect was even more striking and in addition there was a significant increase in stroke volume Neither drug significantly increased cardiac output.[21]

The effect of beta adrenergic blockade on the clinical signs of the disease, in particular the systolic murmur and jerky pulse are difficult to assess and variable The known tendency for the systolic murmur to diminish or disappear with progression of the disease makes the significance of disappearance of the murmur during beta adrenergic blockade difficult to evaluate Thus attention has been focused upon noninvasive techniques as repeatable methods of investigation The use of the apex cardiogram has already been mentioned and studies have been carried out using echocardiography to evaluate the effects of therapy These results have so far been conflicting Thus Shah and co workers [22] reporting on 19 patients on long term oral propranolol therapy found no significant change in mitral valve movement, the systolic opening movement remaining unchanged By contrast, Pridie and co workers,[23] studying patients in the double blind trial already mentioned showed that the form of the mitral echogram became more normal with particular reference to delayed diastolic closure of the mitral valve An increased amplitude of valve movement was also seen and was attributed to an increase in stroke volume The data however, was insufficient to draw any firm conclusions

There seems little doubt that beta adrenergic blockade can improve symptoms particularly in angina and dyspnea There is as yet no evidence that it prevents progression of the disease, though there are theoretical reasons for assuming that it might do so by improving the filling of the left ventricle and by reducing outflow tract obstruction and thereby possibly improving the abnormal patterns of contraction

Surgical treatment has less theoretic appeal but more dramatic clinical effects At the time when it was thought that muscular obstruction to outflow from the left ventricle was the most important, or even the sole manifestation of the disease incision or excision of the hypertrophied muscle appeared a logical procedure Now that more is known of the generalized character of the disease and its important diastolic filling component the operation has less appeal Nevertheless dramatic results have been obtained. Morrow and co workers[24] reported surgical results in 43 patients from a total series of over 200 patients Deep incision of the obstructing muscle and resection of tissue was carried out Pressure gradients ranging from 6 to 175 mm Hg were present before operation between the left ventricle and the aorta at rest in 36 patients There were six deaths in the series systolic gradients were abolished in 27 out of 29 patients studied postoperatively and were minimal in another two patients There was also a decrease in left ventricular end diastolic pressure after operation in 19 out of 21 patients who had increased diastolic pressures preoperatively Mitral

regurgitation was abolished in 11 out of 13 patients. Symptomatic improvement was dramatic and maintained Similar results were reported by Barrat Boyes and O Brien [25] Nevertheless despite these dramatic results the mortality has been uncomfortably high ranging from 25 per cent in earlier series to 10 per cent in more recent series Causes of death have been heart block dysrhythmias and rupture of the ventricle With increasing experience the risk of heart block has become considerably less but other risks remain

Evaluation of the results of surgery have similar difficulties to those of evaluation of medical therapy Hemodynamic studies have certainly suggested striking benefits including improvement in the filling of the left ventricle after surgery It is not known however whether there is any reduction of the left ventricular end diastolic hypertension produced by effort and future post operative studies should include this important information The echocardiographic studies of Shah and co workers[22] showed that after operation the abnormal movement of the anterior mitral leaflet in systole was corrected and the rate of filling of the left ventricle increased suggesting reduction of outflow tract gradient and mitral regurgitation

Since hypertrophic obstructive cardiomyopathy is a generalized, though often patchy myocardial disease it is difficult to understand how a small operation on a localized area of the heart is likely to produce any fundamental improvement However if it is postulated that continuing abnormal patterns of contraction create a vicious circle in which further hypertrophy results in more abnormal contraction patterns then if this vicious circle can be broken by incising or excising portions of the outflow tract hypertrophy might be slowed down and hence the filling characteristics of the ventricle improved It must be admitted that in addition to the adverse effects of beta adrenergic stimulation massive hypertrophy of thick fibrotic muscle must add considerably to the filling problem of the ventricles.

Once the outflow tract obstruction has disappeared and the stage of heart failure has developed then treatment would be directed toward control of the ventricular rate because the absence of atrial drive and the rapid heart rate with short diastolic filling period are both extremely prejudicial to the maintenance of an adequate cardiac output Treatment of this stage of the disease should be with digitalis to slow the ventricular rate An increase in outflow tract obstruction need not be feared since by this time obstruction has usually disappeared completely More important than control of the ventricular rate is the restoration of sinus rhythm and DC counter shock should be carried out as soon as possible and will not infrequently be successful It is most important to start anticoagulant therapy as soon as paroxysmal or established atrial fibrillation develops since the incidence of embolism with atrial fibrillation appears to be higher in hypertrophic cardiomyopathy than in other forms of heart disease known to be associated with this arrhythmia The addition of a small dose of beta adrenergic blockade to assist the control of ventricular rate in addition to digitalis is beneficial Here the dose of beta blockade should be considerably smaller than when used in the earlier stages of the disease the intravenous route should be avoided and amounts as low as 100 mg of practolol twice daily or 10 mg of propranolol four times daily may be used orally

The importance of the preventive aspect of management cannot be too strongly emphasized. The most serious outcome of the disease is sudden unexpected death Apart from this tragedy most patients with HOCM have a long course with often only minor symptoms and gradual deterioration The knowledge that this apparently benign course can be catastrophically interrupted by sudden death at any time constitutes a major challenge to our therapeutic efforts The hope that beta adrenergic blockade would prevent sudden death has not so far been realized though it may have some prophylactic value in this regard and it is much hoped that this is so There is little evidence to suggest any prophylactic effect of surgical treatment but the report of the multicenter trial already quoted that the incidence of sudden death was 7 per cent after surgical treatment as opposed to 18 per cent on beta adrenergic blockade and 16 per cent without treatment respectively is noteworthy and cannot be neglected. Of course it is possible that the omission from the series of patients without outflow tract obstruction who are likely to have a more serious and widespread form of the disease may have resulted in a bias in selection favorable toward surgery However since

surgical treatment is rarely, if ever, applied to patients without outflow tract obstruction the validity of this criticism is doubtful Clearly, a prophylactic role for surgery must now be envisaged and would tend to widen the indications for operation It is known that sudden death is not related to the degree of outflow tract obstruction and may occur as readily in those with, as in those without obstruction so that the role of surgery is likely to be limited in this regard except for the fact that at least 70 per cent of the patients have evidence of obstruction at some time Perhaps resection of the outflow tract muscle may in some way slow down the progress of the disease and diminish abnormal contraction and relaxation

The prevention of other complications of the disease particularly infective endocarditis is also important This is a well known complication, occurring usually on the mitral valve and sometimes having fatal consequences [26] Thus patients with cardiomyopathy should have the same antibiotic prophylactic measures as those with organic heart disease of other types

Pregnancy is well tolerated, and beta adrenergic blockade has not been shown to have adverse effects on mother or fetus[27] though mild heart failure may occur at the end of pregnancy in the former

More information regarding the progress and prognosis of the disease is required before the relative merits of medical and surgical treatment can be fully evaluated and a clear cut policy laid down The present position is summarized below

There is no definite indication for surgical treatment in the absence of outflow tract obstruction and appreciable symptoms Patients with modest outflow tract obstruction and symptoms should be treated with full doses of beta adrenergic blockade and their progress carefully evaluated by repeated clinical assessment and noninvasive techniques of investigation

The occurrence of development of severe symptoms that are associated with persistent substantial outflow tract obstruction (gradient at least 50 mm Hg at rest) with marked bulging of the septum and obstructive features on angiography should be recommended for surgical treatment In view of the findings of the multicenter trial the possibility of extending surgical treatment to patients with less severe symptoms and less severe outflow tract obstruction should be considered, particularly if there has been no symptomatic or objective response to beta adrenergic blockade Mitral valve replacement may be indicated in those rare patients who develop serious organic mitral regurgitation

The management of the substantial number of patients who have the disease without symptoms and with little or no obstruction remains controversial It is logical in view of the theoretical considerations and the results of acute drug studies to put such patients on indefinite beta adrenergic blockade in the hope of preventing progression of the disease and sudden death If this is done however it is very important to follow such patients regularly to see whether any of the abnormal features of ventricular function are returning toward normal Serious side effects of long term beta adrenergic blockade are rare and such a policy appears warranted if facilities for regular and accurate follow up are available In the absence of more definite information the selection of treatment for patients must necessarily be considered on an individual basis The undoubtedly more dramatic effects of surgery must be balanced against the risks of the operation which are higher than the risks of beta adrenergic blockade therapy

Finally if treatment is to be rationalized and convincing long term studies of the progress of the disease are to be achieved nomenclature should be rationalized, and proliferation of new descriptive terms avoided

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varied from 25 to 75 years with an average of 51 The average age for the females was 59 while that of the males was 54 Only six patients (23 per cent) were below the age of 40

Etiology Sixteen patients (62 per cent) had rheumatic heart disease Of these nine (35 per cent) had other associated valvular disease and seven (27 per cent) had isolated aortic regurgitation In eight patients (31 per cent) the etiology was undetermined In one patient a history of lues and positive serologic tests suggested that aortic insufficiency was luetic In one patient a bicuspid aortic valve was considered to be congenital in origin

Symptoms Six patients were symptomatic for less than a year Ten patients were symptomatic from one to five years six patients for six to ten years and three patients for more than ten years One patient was asymptomatic Sixteen patients (62 per cent) had typical or atypical anginal chest pain prior to catheterization Sixteen patients (62 per cent) had symptoms of congestive heart failure such as paroxysmal nocturnal dyspnea orthopnea, or swelling of ankles. Ten patients (39 per cent) experienced palpitations at least once Six patients (23 per cent) had dyspnea only on exertion and four patients (15 per cent) had syncopal episodes Three patients (11 per cent) had only fatigue and one patient (4 per cent) complained of dizzy spells

Functional classification At the time of cardiac catheterization three patients (11 per cent) were in Functional Class IV according to the New York Heart Association classification [9] Fifteen patients (58 per cent) were in Class III seven patients (27 per cent) were in Class II and one patient (4 per cent) was in Class I (Table II)

Physical findings Twenty three patients (89 per cent) had a systolic ejection murmur at the base of the heart radiating to the neck This murmur was graded as II/VI in ten patients III/VI in ten patients and IV/VI in three patients Of the three patients who did not have a systolic ejection murmur two had severe aortic regurgitation one with moderate aortic valve calcification and the other with minimal valve calcification The third patient had a moderate aortic regurgitation with minimal calcification of the aortic valve Seven patients (28 per cent) had an aortic ejection click Twenty two patients (85 per cent) had cardiomegaly

Electrocardiographic findings In nineteen patients (73 per cent) the electrocardiogram showed signs of left ventricular hypertrophy Four patients (15 per cent) had left axis deviation Four patients (15 per cent) had first degree atrioventricular block and five patients (19 per cent) had intraventricular conduction disturbances. Three patients (12 per cent) had signs of left atrial enlargement Five patients (19 per cent) all with associated mitral valve disease had atrial fibrillation Two patients showed electrocardiographic signs of old myocardial infarction One patient had a normal electrocardiogram

Radiographic findings The incidence of detection of aortic valve calcification was higher using image intensification fluoroscopy compared to plain x ray films Findings of plain chest films in twenty five patients and of clinical fluoroscopy in twenty two patients are shown in Table III

Degree of aortic valve calcification and aortic insufficiency Based on findings during cardiac catheterization nine patients (35 per cent) had severe aortic valve calcification eleven patients (42 per cent) had moderate calcification and six patients (23 per cent) had only minimal valve calcification Table IV shows the relation be

Table I Distribution of patients according to age and sex

Age (years)	*All patients*	*Males*	*Females*
21 30	1	1	—
31 40	5	4	1
41 50	7	6	1
51 60	6	6	—
61 70	6	2	4
71 80	1	—	1
Total	26	19	7

Table II Etiology of aortic insufficiency

Etiology	*All patients*	*Males*	*Females*
Rheumatic heart disease			
Isolated aortic insufficiency	7	6	1
Aortic and mitral valve disease	8	5	3
Aortic mitral and tricuspid valve disease	1	—	1
Congenital biscupid valve	1	1	—
Luetic aortic insufficiency	1	—	1
Undetermined etiology	8	7	1

Clinical communications

Calcific aortic insufficiency—a review of 26 patients

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Calcification of the aortic valve is usually associated with aortic stenosis and occurs in congenital bicuspid aortic valves [1] in rheumatic aortic valvulopathy,[2] and in degenerative valvulopathy of older age [3-5] Such patients usually have systolic ejection murmurs over the aortic valve area radiating to the neck The purpose of this report is to describe twenty six patients with aortic systolic ejection and diastolic blowing murmurs with calcification of the aortic valve who were found to have pure aortic insufficiency without aortic stenosis that is calcific aortic insufficiency without aortic stenosis A similar group of patients has not been previously described to our knowledge

Materials and methods

Our patient material includes a wide unselected spectrum of heart diseases, mainly in adults referred for diagnostic studies and therapeutic considerations We demonstrated some degree of aortic regurgitation by supra aortic valve contrast cineangiography in two hundred forty two patients over a four year period from Jan 1969 to Dec 1972 Many of these patients also had other valvular pathology including associated aortic stenosis However of all patients with any degree of aortic valve disease we found twenty six patients (10 7 per cent) with pure aortic insufficiency with calcification of the aortic valve There was no aortic stenosis gradient in twenty three patients We have also included three patients who had peak aortic gradients of 3, 10, and 18 mm Hg with mean gradients of 3 7 and 15 mm Hg, respectively Moderate and severe aortic insufficiency alone may have accounted for these gradients Complete clinical and hemodynamic data were compiled for these patients Patients with isolated aortic insufficiency were considered of rheumatic etiology only if they had a history of definite rheumatic fever or demonstrated associated mitral stenosis One patient had probable congenital aortic valve disease demonstrated by a bicuspid valve Other patients with isolated aortic regurgitation without history of rheumatic fever were considered as having aortic insufficiency of undetermined etiology [6,7] The degree of aortic valve calcification was determined during cardiac catheterization utilizing horizontal image intensification fluoroscopy and cineangiography Calcification was classified as *severe* in patients with dense continuous calcification of all areas of the valve as *moderate* when dense discontinuous patches of calcification were found in one or more areas of the valve and as *minimal* when discontinuous flecks were found Aortic regurgitation was graded on a 0 to 4+ scale [8] Severe aortic regurgitation was graded 3 or 4+ moderate regurgitation 2+, and minimal regurgitation 1+

Results

Sex and age Of the twenty six patients nineteen (73 per cent) were males and seven (27 per cent) were females Distribution according to age groups is shown in Table I Patient age range

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Table V Distribution of patients according to cardiac index and left ventricular end diastolic pressure

		Total		Isolated aortic insufficiency	Aortic insufficiency plus mitral valve disease
		No	%		
Cardiac index	<2 5 L/min/M²	16	67	7	9
Cardiac index	>2 5 L/min/M²	8	33	7	1
LVEDP	≤ 12 mm Hg	9	35	3	6
LVEDP	> 12 mm Hg	17	65	6	11

Cardiac index was determined only n 24 patients.

has a higher degree of wear and tear It is also possible that calcification of the aortic valve with deformities caused by rheumatic or luetic valvulitis is more frequent because of the higher degree of wear and tear of such valves The mechanism and histopathology of aortic valvular calcification has been studied[3,18] but does not contribute to the explanation of the cause of this process We found aortic valve calcification in six patients younger than 40 years of age The average age was only 51 years and 62 per cent of the cases were of rheumatic etiology These facts suggest that calcification in a relatively younger age is related to an earlier wear and tear process of the previously deformed valve rather than to a degenerative process related to aging In this series only one patient had probable luetic aortic regurgitation Five had a history of subacute bacterial endocarditis This distribution fits the decline of syphilis as the cause of aortic insufficiency[19,20] and the recent rise in subacute bacterial endocarditis as a cause of aortic insufficiency[11] Most of the patients exhibited evidence of cardiomegaly either at the time of physical examination or by chest radiography Many also had an electrocardiographic evidence of left ventricular hypertrophy

The best method for detection of aortic valvular calcification is cardiac fluoroscopy particularly horizontal image intensification fluoroscopy[14] We detected aortic valve calcification in only 16 per cent of the cases by plain chest films but in 68 per cent by image intensification fluoroscopy An additional 32 per cent were detected only during cardiac catheterization utilizing image intensification fluoroscopy and cineangiocardiography The relative high incidence of calcification which was not detected by routine clinical fluoroscopy is partially explained by the fact that 23 per cent of the patients had minimal valvular calcification

Almost all of our patients (96 per cent) had severe and moderate aortic insufficiency and most of them were in Functional Class III or IV Most had poor left ventricular contractility and reduced cardiac indices as well as elevated left ventricular end diastolic pressures The high incidence (88 per cent) of aortic systolic ejection murmur is not surprising in calcific aortic insufficiency However the association of this murmur with a calcific aortic valve led to the misdiagnosis of aortic stenosis in more than half of the cases prior to catheterization Our experience shows that not every aortic valve which is calcified (even with an associated ejection murmur) is necessarily a stenotic valve Awareness of calcific aortic insufficiency may increase the accuracy of clinical diagnosis

Summary

Twenty six patients 8 3 per cent of all patients with aortic valve disease and 10 7 per cent of all patients with any degree of aortic insufficiency detected in our catheterization laboratory had pure calcific aortic insufficiency (no associated stenosis) Nineteen (73 per cent) males and seven (27 per cent) females ranged in age from 25 to 75 years of age (mean 51) Twenty three per cent were younger than 40 Sixteen (62 per cent) had rheumatic heart disease one had luetic aortic valve disease one had congenital bicuspid valve and eight (31 per cent) had aortic insufficiency of undetermined etiology Twenty three patients (89 per cent) had an aortic systolic ejection murmur and seven (28 per cent) had an aortic ejection click Aortic valve calcification was detected by plain chest films in only four patients (16 per cent) and by routine image intensification fluo

Table III Findings in chest films in 25 patients, and on image intensification fluroscopy in 22 patients

	Plain chest films		*Fluroscopy*	
	No	*%*	*No.*	*%*
Cardiomegaly	23	92	18	82
Calcification of aortic valve	4	16	15	68

Table IV Distribution of patients according to degree of aortic valve calcification and to degree of aortic regurgitation

Degree of calcification \ *Degree of regurgitation*	*Severe*	*Moderate*	*Minimal*	*Total*
Severe calcification	8	1	–	9 (35%)
Moderate	8	2	1	11 (42%)
Minimal	4	2	–	6 (23%)
Total	20 (77%)	5 (19%)	1 (4%)	

tween degree of aortic regurgitation and the degree of calcification

Misdiagnosis of aortic stenosis Aortic stenosis was diagnosed clinically as the predominant lesion in fourteen patients (54 per cent) subsequently proved to have pure calcific aortic insufficiency Eleven of these patients had no aortic valve gradient Three patients had a peak systolic gradient of 3 10 and 18 mm Hg Isolated aortic stenosis was misdiagnosed in one patient prior to catheterization

Left ventricular function Nineteen patients (77 per cent) had reduced left ventricular contraction as determined by ventriculography[10] Six patients had a normal ventriculogram and in one patient, left ventriculography was not performed Sixteen patients (67 per cent) had a low cardiac index and seventeen patients (65 per cent) had elevated left ventricular end diastolic pressure Cardiac indices and left ventricular end diastolic pressures are shown in Table V

Coronary arteriograms Selective coronary arteriography was performed in twenty one patients Eighteen patients (86 per cent) had normal coronary arteries, while three patients (14 per cent) had obstructive coronary artery disease

Discussion

Calcification of the aortic valve is commonly associated with aortic stenosis[2 11 12] It is less common in patients with combined aortic stenosis and insufficiency, and has been thought to be unusual in patients with pure aortic insufficiency[11 13] The severity of calcification is correlated well with the transvalvular systolic gradient[13] In patients with aortic stenosis and insufficiency the amount and severity of calcification has been correlated with the systolic gradient but not with the degree of regurgitation[13] The entity of calcific aortic stenosis is so familiar that some authors have suggested that if aortic valve calcification is demonstrated in a patient with aortic regurgitation the presence of associated aortic stenosis may be inferred[11]

Our series of twenty six patients with pure aortic insufficiency and aortic valve calcification documents the existence of calcific aortic insufficiency The combination occurred in 8 3 per cent of all aortic valve pathology diagnosed in our laboratory, and in 10 7 per cent of all cases with aortic insufficiency with or without stenosis. Of course the incidence of aortic valve calcification in patients with aortic stenosis is much higher and according to some authors, is 85 to 90 per cent[13 14]

The preponderance of males (73 per cent) having calcific aortic insufficiency is compatible with the general higher incidence of aortic valve disease in males as opposed to mitral valve disease[11 12] Calcification of the aortic valve is thought to be correlated with advanced age,[15] even though Glancy and co workers[13] found that the severity of calcification did not correlate with age The average age of our patients was 51 years and almost a quarter of the patients were younger than 40 The etiology of calcific aortic stenosis was originally attributed to healing of rheumatic valvulitis[2] Other etiologies such as congenital bicuspid valves and degenerative changes have been described more recently[6 7 15 17] Calcification of the aortic valve may be a result of wear and tear of the valve a degenerative process in character[4] It is possible that calcification of the congenital bicuspid aortic valve is more frequent since this kind of valve

Acute transmural myocardial infarction associated with active Coxsackie virus B infection

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The Coxsackie virus B group are known to cause human heart disease in particular myopericarditis It has also been suggested that they may play a part in the production of congenital heart disease obscure cardiomyopathies and valvular disease Animal experiments have demonstrated that all tissues of the heart may be affected and since valvulitis indistinguishable from that due to rheumatic fever can be consistently produced by these agents it has been postulated that there may be a synergism between virus and streptococcus[1]

Initially Coxsackie virus B myocarditis was thought to be confined to the very young but adult cases have been reported with increasing frequency ever since Fletcher and Brennan[2] first described an adult with pericarditis due to this agent The human heart may be affected much more frequently than is generally realized since Burch and co workers[3] using the fluorescent antibody technique demonstrated Coxsackie virus B antigen in almost one third of the series of 55 hearts studied at routine autopsy all those showing the antigen had evidence of focal myocarditis Most of the work has been done on the Coxsackie virus B as this is the easiest to study but other viruses are also known to be cardiotropic notably Coxsackie A and some members of the Echo family[4] The full extent of viral heart infection is a matter for speculation

Most clinical studies have been concerned with cases of myocarditis or pericarditis In adults the differentiation between myopericarditis and myocardial infarction is not always easy especially when the infarction is subendocardial Both illnesses present with similar types of pain and the electrocardiographic (ECG) changes of pericarditis may be very hard to distinguish from those of infarction particularly if the early characteristic changes of the former are not recorded The presence of a pericardial rub in the absence of full thickness infarction is said to favor the diagnosis of myopericarditis[5] but when this is absent and only the myocardium is involved the differentiation between infarction and infection is difficult to distinguish It may be of importance that in several of the clinical series there have appeared reports of cases more suggestive of infarction than myocarditis[5,6]

Because it seems that viral disease of the heart may not be confined only to obvious cases of myopericarditis the authors have been studying the incidence of active Coxsackie virus B infection in patients with all forms of heart disease admitted under their care In an earlier paper[7] the results obtained over the first year showed that approximately 11 per cent of all patients with acute heart disease had evidence of active Coxsackie virus B infection at the time of their admission The work was continued for almost three years and out of the total of 734 patients studied an acute enteroviral infection has been found in 68 of these patients Some were undoubtedly suffering from myopericarditis but a proportion had been diagnosed on clinical grounds as having myocardial infarction When the results of the viral tests became available invariably after the patient had left the hospital a re assessment was made In some patients origi

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roscopy (before catheterization) in fifteen patients (68 per cent) The remaining 32 per cent had the calcification of the aortic valve detected during catheterization

Aortic valve calcification was severe in nine patients (35 per cent), moderate in eleven patients (42 per cent) and minimal in six patients (22 per cent) Aortic insufficiency was severe in twenty patients (77 per cent), moderate in five patients (19 per cent) and minimal in one patient (4 per cent) Nineteen patients (77 per cent) had reduced left ventricular contractility Sixteen patients (67 per cent) had low cardiac index Eighteen patients had normal coronary arteries and three patients had obstructive coronary artery disease Aortic stenosis was misdiagnosed as the predominant lesion in fourteen patients (54 per cent)—prior to catheterization This series demonstrates that all patients with calcified aortic valve disease and with ejection murmurs do not *necessarily have aortic stenosis Pure calcific aortic insufficiency* is a distinct entity more common than previously suspected

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Table III

Patient No	Age Sex	Infarction site	Pericardial rub	Prior Flu	Complications	Hypertension	Previous infarction	Coxsackie virus Antibody Titers: Rising	Coxsackie virus Antibody Titers: Fixed	Follow up and time (months)	Further infarction
1	45 M	Ant	+	–	VF	–	–	B4 40 640	B2	–	No
2	59 M	Ant.	–	–	–	+	–	B3 10-40	–	–	No
3	54 M	Ant	–	+	Re inf	–	–	B4 10 40	B1 B4	N/C (30)	Yes
4	45 M	Ant	–	–	Re inf	–	–	B3 10-40	–	–	N/K
5	58 M	Ant	–	–	Re inf	+	–	B2 20 80	B2,B4	–	Yes
6	40 M	Ant	+	–	–	–	–	B3 10-40	–	N/C (18)	Yes
7	57 M	Post	–	–	Re inf	–	+	B2 20 80	–	–	N/K
8	49 M	Ant	–	+	RCP	+	–	B4 80 320	B2	N/C (9)	No
9	37 M	Ant.	–	–	–	–	–	B5 40 160	B2,B4	N/C (15)	Yes
10	43 M	Post.	–	–	–	–	–	B4 40 160	–	–	Yes
11	64 M	Post	–	–	–	–	–	B4 10 40	B2	–	No
12	60 M	Post	–	–	–	+	–	B5 10 40	B4	–	Yes
13	64 F	Ant	–	–	RCP	+	–	B2 20 80 B3 40 160	B1 4 5	–	Yes
14	49 M	Ant	–	+	VF	+	+	B4 40 160	B2	–	Yes fatal
15	65 M	Ant	–	–	–	–	–	B2 20 160 B3 0 80 B4 0 160	–	–	No
16	54 M	Post	+	–	–	–	–	B1 0 160 B3 0 80	–	–	No
17	46 M	Ant	–	–	VF	–	–	B3 40 320	–	–	No
18	47 M	Post	–	–	–	–	–	B2 40 160 B5 20 160	–	–	No
19	68 M	Post	+	–	VF	–	–	B5 80 320	–	–	No
20	54 M	Post	–	–	CVA	–	–	B5 40 160	B2 3 4	–	No

Abbreviation ant. anterio post. posterior VF ventricular fibrillation Re i f e infa ction RCP repeated chest pain N/C no change N/K not known and CVA trans ent cereb al symptoms

20 had evidence of active Coxsackie virus B in fection a rate of 8 6 per cent Thirty seven (16 per cent) of the 233 cases with infarction oc curred in women (Table I)

Ages and sex of patients Fourteen (70 per cent) of our 20 patients with active Coxsackie virus B infection were aged between 45 and 64 years the youngest subject was 37 the oldest 68 Only one patient was a female However the number of patients involved appears too small to draw any significant conclusions from this fea ture (Table II)

Types of virus involved Twenty five active virus infections were found in the 20 patients concerned Three patients showed significant rises in titer to two types of Coxsackie virus B si multaneously and in one patient rises in titer to three strains were found. With the exception of Coxsackie virus B1 there was a fairly even dis tribution of cases between the remaining four types (Table III)

Pericardial friction rubs were heard in four pa tients. In two patients the rubs were prolonged for 10 and 11 days respectively and in both pa tients the temperature remained elevated for ap proximately the same period. Although the fric tion rub in infarction is often short lived it may when the infarction is large[8] persist for many days

Ventricular fibrillation developed in two pa tients after admission and in another patient repeated attacks of ventricular tachycardia and fibrillation occurred on the fifth seventh and ninth days In the fourth subject one of the men with a prolonged pericardial rub ventricular fibrillation occurred on the twentieth day with out warning A fifth patient (Case No 9) who re covered from his original infarction uneventfully was re-admitted 18 months later with a further infarction and developed ventricular fibrillation one hour after admission All of these patients were successfully resuscitated.

There were no deaths in hospital in this series but a man (Case No 14) who had had repeated at tacks of ventricular fibrillation was admitted in a dying condition three months later Autopsy

Table I Ages and sex of patients

Ages	Male	Female
35 44	3	0
45 54	8	0
55 64	5	1
65 +	3	0
	19	1

Table II *Types of virus involved*

	Cases
Coxsackie virus B1	1
Coxsackie virus B2	5
Coxsackie virus B3	6
Coxsackie virus B4	7
Coxsackie virus B5	6
	25

nally considered to have had subendocardial infarction it seemed possible we had misdiagnosed myocarditis but, in other patients all the evidence pointed to infarction

One of the most notable findings was that a substantial number of patients had the signs and symptoms of transmural infarction a picture not usually associated with viral infections The significance of this is not yet clear but it does raise the possibility that infection with a cardiotropic virus may have some relationship to myocardial infarction The purpose of this paper is to report the clinical features of 20 of our patients with acute transmural myocardial infarction who concurrently had an active Coxsackie virus B infection

Criteria for diagnosis

Myocardial infarction All these patients presented with chest pain thought to be of cardiac origin The diagnosis of transmural infarction was substantiated by characteristic ECG changes which were evolutionary in nature and resulted in the inscription of pathologic Q or QS complexes in the appropriate leads In all our patients, the serum glutamic oxaloacetic transaminase was elevated in the acute phase of the illness and in the great majority of patients there were also significant rises in the serum lactic dehydrogenase and serum creatine phosphokinase

Active Coxsackie virus B infection We attempted unsuccessfully to culture viruses from throat swabbings and feces in the first 12 of our cases Thereafter it became impossible for technical reasons to send further specimens for culture and the diagnosis of viral infection has therefore, been made on serologic findings

All sera were examined for neutralizing antibodies against Coxsackie virus B, Type 1 through 5 An active infection was only diagnosed when there was a fourfold or greater rise in antibody titer between the serum collected immediately after admission and the serum collected during convalescence at least two weeks later Smaller rises in titer or high but static titers in both specimens were not regarded as evidence of acute infection Since the rise in titer occurs very early in the illness the diagnosis may be missed if there is any delay in the collection of the initial specimen so our figures probably underestimate the true rate of active viral infection

Virus serology The presence of Coxsackie virus antibody in patients' sera was demonstrated by neutralization of seed virus of Coxsackie virus B, Types 1 through 5, in tissue culture using mycoplasma free FL amnion cells (Flow Laboratories) in Eagle's basal medium fortified with 5 per cent fetal calf serum and protected from bacterial contamination with 100 units per milliliter of penicillin and streptomycin Equal volumes of dilutions of patients serum (inactivated for 30 minutes at 56° C) and virus seed containing 100 TCD 50 per milliliter were incubated in flat bottomed microtiter plates at 37° C for 1 hour Approximately 6,000 FL amnion cells in 0 05 ml volumes were added and the microtiter plates incubated in a moist atmosphere at 37° C for 3 to 4 days Hepes buffer was used in preparing dilutions thus avoiding the need for 5 per cent CO_2 in the incubation period. Using this technique, a screening test on 1/20 dilution of a patient's second serum sample for the presence of neutralizing antibody was carried out as a preliminary for testing in parallel with a dilution range 1/10 through 1/5120 Titration end point was indicated as the highest dilution of serum allowing the development of a monolayer of cells in the presence of virus

Results

Of the 734 patients admitted with presumed heart disease there were 233 patients who fitted our criteria for transmural infarction Of these

his study of the records of the London Hospital was unable to find any evidence of progressive deterioration of the coronary arteries over the forty years prior to 1949 a period during which the incidence of myocardial infarction increased rapidly

There must therefore be doubt as to whether thrombosis and coronary atherosclerosis alone can account for the present epidemic of myocardial infarction Possibly there are other agents as yet unknown which cause or precipitate infarction in susceptible subjects The reaction to infection by a cardiotropic virus might be one such agent

Some viral illnesses notably poliomyelitis have changed considerably over recent years presumably due to alterations in the hosts immunity It would not be surprising if illness due to Coxsackie virus a close relation of the poliovirus also changed in character for the same reason

Experimental work has shown that many forms of cardiac trauma condition the heart to make it more susceptible to a virus attack and, in humans it has been suggested that hypertension and coronary atherosclerosis act as conditioning factors[11] If this is the case then a change in the immunologic state of a population could be attended by an increase in the incidence of virus disease of the heart The action of viruses on the heart is incompletely understood but possibly in addition to causing myocarditis other mechanisms such as autoimmunity could operate and lead to illnesses resembling myocardial infarction

As Coxsackie virus B infection was found in almost a tenth of our patients with transmural infarction and as several other viruses are known to affect the heart it seems a matter of concern to establish what part if any viruses play in the causation of myocardial infarction With the modern techniques now available this might prove to be a most rewarding field to study

Summary

Out of a total of 233 patients suffering from transmural myocardial infarction 20 patients were found to have serologic evidence of a concurrent active Coxsackie virus B infection While the infection may have been coincidental it is also possible that the virus may have played some part in the illness Conceivably myocarditis could be mistaken for infarction or by some mechanism as yet unknown the virus might precipitate infarction in susceptible subjects

We wish to thank Sister J Smith and the staff of the Coronary Care Unit together with Mrs J Musk, Mr J Reeby and Mr G Lace of the Fremantle Hospital Laboratory without whose help it would not have been possible to carry out this study We also wish to express our appreciation to Drs. Hobday and Joachim and the staff of the Virus Laboratory who carried out the very large number of tests for us

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confirmed the presence of severe coronary artery disease associated with both old and new myocardial infarction In addition on microscopy, there was diffuse interstitial edema with scattered groups of inflammatory cells mainly lymphocytes These were not directly related to the ischemic lesions and the possibility of a myocarditis due to his Coxsackie B4 infection superimposed on the ischemic lesion could not be ruled out The 100 per cent survival rate could suggest that these illnesses were milder than usual However to be included in this study, patients had to have survived at least two weeks after admission by which time the most dangerous period had passed

Only three patients gave a history of a preceding febrile illness and in hospital no clinical evidence to suggest a concurrent viral infection was found except in one subject (Case No 19) who developed hepatitis Whether the hepatitis was due to the viral infection was hard to determine For a week while the jaundice was developing he ran a fever which subsided immediately after his procainamide was stopped Until his virus tests became known we had assumed that his fever and jaundice were toxic reactions to the drug Apart from the three patients already described no subject ran a temperature for more than five days

The serum cholesterol levels were elevated to above 250 mg per cent in seven out of the 19 patients in whom it was measured One man (Case No 20) presented in hospital with cerebral symptoms These rapidly disappeared and he was then found to be suffering from myocardial infarction This symptom was thought to have been due to transient cerebral ischemia consequent upon his infarction

We were able to repeat the serum antibody titers of four patients after they had been discharged from hospital there was no change in the titers to the various Coxsackie virus B types over periods ranging from nine to 30 months

While the evidence of acute enterovirus infections in the series is based on established criteria viz a fourfold or higher rise in titer between first and second serum samples separated by at least a fortnight the finding in cases 13 15, 16 and 18 where two or more viruses appear associated requires comment Anamnestic responses may account for these heterologous titers rather than a concurrent infection by distinct types of Coxsackie virus B There is no ready explanation for the apparent idiosyncrasy in these patients but it is possible that, when a concurrent rise in titer has occurred to more than one type, the finding came about as the result of stimulation of a virus persisting in the tissues from a past infection

Discussion

In this paper we have discussed only those patients with unequivocal evidence of infarction They accounted for less than one third of the patients in our whole series who had a Coxsackie virus B infection The symptoms of all these patients appeared to range over a broad spectrum of illnesses associated with chest pain starting with Bornholm disease moving through myopericarditis to subendocardial infarction, and ending at the other extreme in transmural infarction Clinically there were no clear cut boundaries to separate the different groups with heart disease

These 20 patients with full thickness myocardial infarction and concurrent virus infection did not seem to differ in any way from other patients with a similar degree of infarction but no demonstrable virus infection The illnesses were just as severe and although there were no hospital deaths in our series, this was entirely due to modern resuscitative measures without these the mortality rate would have been 20 per cent The 40 per cent re infarction rate in less than three years is also high

It is difficult to interpret the results but there seem to be three main possibilities First as Coxsackie virus infections are common and often subclinical the association with infarction may be coincidental Second the ECG changes of transmural infarction could have been produced by the electrical silence of large areas of myocarditis Third, the virus by some means as yet unknown could have precipitated or even caused infarction

The etiology of myocardial infarction remains obscure the generally accepted view that it is due to thrombotic occlusion of a diseased vessel has come under attack and recent work has shown that in some cases the thrombus follows rather than precedes the infarction [9] Also should there not have been a great increase in the incidence of severe coronary artery disease over the last half century to coincide with the rise in the rate of myocardial infarction? Yet Morris [10] in

cent) an arrhythmia was present postoperatively which was not present preoperatively A total of 79 different arrhythmias in these 37 patients was noted (Table I) The most common arrhythmias in all groups combined were atrial fibrillation and frequent ventricular premature contractions The arrhythmias noted in the various surgical groups are listed in Table II Rhythm disturbance was noted more frequently in the patients undergoing valvular surgery (26 out of 27) than in those with coronary artery bypass (6 out of 15) ($p < 0.001$) In the aortic valve group the most common arrhythmias were atrial fibrillation and bundle branch block For those with mitral valve surgery atrial fibrillation and junctional rhythm occurred most often Atrial fibrillation and junctional rhythm were noted with equal frequency following double valve surgery whereas atrial fibrillation and ventricular premature contractions were the most frequent arrhythmias in the coronary artery bypass group

Electrolyte changes No relation between changes in serum sodium or potassium and arrhythmia was noted beyond the immediate operative period No abnormalities of sodium were noted other than for one patient with pre and postoperative hyponatremia Potassium levels were well maintained within normal limits either by intravenous infusion of KCl or exchange resin or dialysis in those patients with acute renal failure It was frequently noted however that various arrhythmias were present immediately upon termination of cardiopulmonary bypass These were frequently correlated with hypokalemia and were generally controlled rapidly by the infusion of intravenous potassium chloride These consisted of ventricular premature contractions atrioventricular dissociation with junctional tachycardia as well as junctional bradycardia The preoperative and postoperative levels of calcium and magnesium are shown in Fig 1 The mean level of calcium fell by postoperative Day 2 and remained depressed at postoperative Day 5 Calcium fell in 20 out of 30 patients in whom measurements were obtained, and 17 of these had an arrhythmia This contrasts with 7 out of 10 patients with normal postoperative calcium who developed an arrhythmia (p not significant) The fall in calcium paralleled the fall in serum albumin concentration noted postoperatively in 14 out of 17 patients in whom it was measured Magnesium fell to abnormally low values in 8 out of 19 patients where measured (Fig 1) The lower limit of serum magnesium for our laboratory is 1 8 mg per cent The levels tended to fall by postoperative Day 1 and returned to normal by postoperative Days 3 to 4 Whereas all patients with low magnesium had an arrhythmia 8 out of 11 with normal magnesium also demonstrated postoperative rhythm disturbance (p not significant) There were no patients with clinical evidence of hypocalcemia or hypomagnesemia

Table I Arrhythmias following cardiac surgery 50 patients

Arrhythmia	*No. patients with arrhythmia*		
	Postoperative		*Preoperative*
I *Supraventricular*			
APC s (>10/min)	6		0
Atrial fibrillation	24		13
Atrial flutter	3		0
Junctional rhythm	5		0
Junctional tachycardia†	3		0
Junctional bradycardia‡	6		1
Atrial tachycardia	5		1
Total	52	66%	
II *Ventricular*			
VPC s (> 10/min)	13		2
Ventricular tachycardia	1		0
Ventricular fibrillation	1		0
Total	15	19%	
III *Disorders of atrioventricular and intraventricular conduction*			
Second degree heart block	1		1
Third degree heart block	1		0
A V dissociation	5		1
RBBB	2		1
LBBB	3		2
Total	12	15%	

Abbreviations APC atrial premature contraction LBBB left bundle branch block RBBB right bundle branch block and VPC ventricular premature contraction

Ventricular rate 60 100/min

†Ventricular rate > 100/min

‡Ventricular rate < 60/min.

Arterial blood gases Arterial pH and P_{CO_2} were well maintained within normal limits in the majority of patients postoperatively No correlation with arrhythmia was noted.

Creatinine clearance The mean values for creatinine are shown in Fig 1 Creatinine clearance fell greater than 10 ml per minute in 38 out of 42 patients where complete measurements were available It was still depressed after postoperative Day 2 in 25 out of 42 patients Acute renal failure was noted in three patients requiring dialysis in two patients

Arrhythmias following cardiac surgery relation to serum digoxin levels

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Arrhythmias constitute one of the most significant causes of morbidity and mortality in patients undergoing cardiac surgery Many factors may play a role in the genesis of these arrhythmias and several of these are reviewed in the present paper In particular, special attention is paid to the role of electrolyte abnormalities, pericarditis serum osmolarity digoxin level and the type of surgery performed.

Fifty patients selected at random from those undergoing cardiac surgery at New York University Hospital from August 1972 to April 1973 were selected for study There were 11 patients with aortic valve replacement, 12 with mitral valve surgery 4 with double valve surgery 15 with coronary artery bypass and 5 with coronary artery bypass and associated valve replacement, and 3 with miscellaneous procedures (removal left atrial myxoma closure of ventricular septal defect (VSD), and left ventricular aneurysmectomy) included in the study group One day preoperatively serum blood urea nitrogen creatinine sodium potassium calcium magnesium, and albumin were obtained as was a 24 hour urine collection for creatinine Cardiac rhythm was monitored for four hours and any arrhythmia was noted Postoperatively clinical evaluation was performed from the time the patient reached the recovery room until discharge Arrhythmias were detected from bedside monitoring Serum sodium, potassium, creatinine and arterial blood gases were followed for five days postoperatively In some patients serum calcium magnesium, and albumin were obtained on postoperative Days 1 through 5, as was a 24 hour urine for creatinine clearance Serum digoxin levels performed by the radioimmunoassay method of Smith and Haber[2,3] were obtained on patients who had received digoxin up to three days prior to surgery This assay, dependent upon the beta detection of tritium, will give slightly different results than gamma detection systems employing a radioiodine tag Preoperative specimens were obtained 24 hours prior to surgery and the postbypass specimen obtained 12 to 22 hours following surgery Repeat levels were obtained when patients received additional digoxin postoperatively Specimens were obtained at least eight hours after the last dose of digoxin Serum osmolarity was measured 24 hours preoperatively and on postoperative Days 1 through 3 in the majority of patients

Serum sodium potassium, and urea determinations were performed on the SMA 6 system and magnesium and calcium by atomic absorption on the Perkin Elmer Model 306 Serum osmolarity was determined on an Advanced Instruments osmometer by freezing point depression

All patients underwent cardiopulmonary bypass The pump oxygenator was primed with 2 000 ml of Ringer s lactate solution and 1 000 to 1 500 ml of citrated blood In addition 0 6 Gm of calcium chloride were given for each 500 ml of citrated blood and 1 0 Gm of magnesium sulfate and 10 mEq of potassium chloride were added Fifty per cent glucose (12 5 Gm) was added to the oxygenator

Results

Postoperative arrhythmias Thirty seven out of 50 patients (74 per cent) had at least one postoperative arrhythmia In 28 patients (56 per

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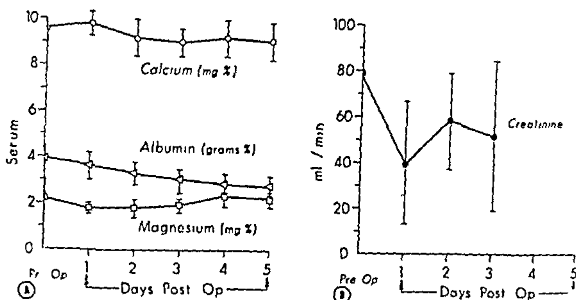


Fig 1 A Mean pre and postoperative serum calcium albumin and magnesium B mean pre and postoperative serum creatinine clearance

Table II Arrhythmias in patients with valvular and coronary bypass surgery

				Postoperative arrhythmias							
Surgical group	*No patients*	*No patients preoperative arrhythmia*	*No patients postoperative arrhythmia*	*Atrial fibrillation*	*Atrial flutter*	*Junctional rhythm**	*PAT*	*vpc†*	*3°HB*	*A V dissociation*	*BBB*
AVR	11	5	10	6	0	2	1	3	0	0	2‡
MVS	12	8	12	9	1	7	2	3	0	2	0
AVR + MVS	4	1	4	3	1	3	1	2	0	1	1
CAB	15	1	6	4	1	1	0	3	0	1	0
CAB + Valve surgery	5	2	3	2	0	1	0	2	0	0	0
Miscellaneous	3	1	2	0	0	0	1	1	1	1	1
	50	18	37	24	3	14	5	15	1	5	4

Abbreviations AVR aortic valve replacement BBB bundle branch block CAB coronary artery bypass MVS mitral valve surgery PAT paroxysmal atrial tachycardia VPC ventricular premature contractions and 3 HB third degree heart block
*Includes patients with junctional tachycardia and junctional bradycardia
†Includes 1 patient with ventricular tachycardia
‡One patient alternated from right to left bundle branch block

Serum osmolarity Serum osmolarity was measured in 43 patients Thirty four patients had wide shifts (greater than 10 mOsm per liter) in osmolarity Postoperative values were elevated in 17 patients and depressed in another 17 patients Twenty two of these 34 patients demonstrated postoperative arrhythmia where 7 out of 9 with stable postoperative osmolarity developed a rhythm disturbance (p not significant)

Pericardial rubs Although transient pericardial rubs were noted in 46 per cent of the patients no correlation with arrhythmia was noted

Serum digoxin levels Preoperative and postoperative digoxin levels for the 12 patients who were maintained on digoxin until 2 to 3 days prior to surgery, and for whom complete measurements were obtained are listed in Table III Postoperative levels of 0 75 ng per milliliter or greater were detected in Patients 8 through 12 and the levels for Patients 10 through 12 are

Table III Serum digoxin levels pre and postcardiopulmonary bypass

Patient	No days digoxin discontinued prior to surgery	Maintenance dose (mg)	Digoxin levels (ng/mL) Preoperative	Digoxin levels (ng/mL) Postoperative
1 MR	3	0/25 OD	0	0
2 BM	3	0/25 BID	0 48	0
3 LB	3	0/25 OD	0 45	0 22
4 FP	2	0/25 OD	0 43	0 30
5 FO	2	0/25 OD	0 41	0 35
6 SW	3	0/25 BID	0 8	0 44
7 BZ	2	0/25 OD	1 0	0 6
8 FB	2	0/25 OD	1 35	0 75
9 CA	2	0/25 BID	1 15	0 83
10 JG	2	0/25 BID	1 25	1 20
11 PF	2	0/25 OD	1 55	1 25
12 JC	2	0/25 BID	1 45	1 35

within the therapeutic range as determined by this assay[2,4] The postoperative levels were reduced in all patients in comparison to pre operative values

Discussion

Frequency and distribution of arrhythmias The incidence of arrhythmias following cardiac surgery has been reported in a range of 29 to 74 per cent of patients studied. The frequency of arrhythmia in this series (74 per cent) is identical to the results of Smith s series[1] The higher incidence in the present series as compared to earlier retrospective works may be related to the high degree of surveillance which was achieved in this report In addition this series included all arrhythmias including frequent ventricular and atrial premature contractions and those arrhythmias noted preoperatively with recurrence post operatively There is a similarity in the distribution of arrhythmias among the various reports with atrial fibrillation most common and junctional rhythm next The majority (78 per cent) of arrhythmias in this series occurred within the first two postoperative days. Smith and co workers[1] noted a higher incidence of conduction disturbance in patients with aortic valve replacement compared to those with mitral valve surgery In this series, only 2 out of 11 with aortic valve replacement had bundle branch block and the incidence of supraventricular arrhythmias was similar to the mitral group The higher incidence of arrhythmias in the valvular surgery group may be related to the more extensive surgical trauma accompanying valve replacement

Electrolyte changes osmolarity and creatinine clearance As in Smith and co workers series[1] no relation between arrhythmia and serum sodium and potassium values was noted after the patient left the operating room Serum magnesium levels have been shown to be reduced following cardiopulmonary bypass[8] as a result of dilution from the prime solution In addition increased urinary excretion of magnesium following general surgery[9,10] has been noted. The early fall in magnesium noted in 8 out of 19 patients in this series and the return to normal by postoperative Days 3 to 4 suggest dilution from the prime as the mechanism of hypomagnesemia Although both supraventricular and ventricular arrhythmias[11,12] have been described in patients with hypomagnesemia no relation was noted in this group of patients Serum calcium levels fell below normal limits in 20 out of 30 patients in this series but no relation to arrhythmia was noted Reduced levels of serum calcium following general surgery have been related to the effects of transfusion of large amounts of citrated blood,[14] or to the effects of increased fecal loss[15] The reduced levels noted in this series were probably related to the fall in serum albumin levels noted postoperatively the cause for the latter cannot be ascertained from this data Although wide shifts in serum osmolarity were noted postoperatively undoubtedly secondary to the use of dilute prime with a

Table IV Serum digoxin levels in patients with postoperative junctional rhythm or A V dissociation

Patient	Rhythm: Preoperative	Rhythm: Postoperative	Digoxin level during arrhythmia (ng/mL)
1 JG	NSR	(NSR+JR) AVD	0
2 IB	NSR	(NSR+JR) AVD	0
3 RM	AF	JB	0
4 FS	NSR	JT	0
5 FP	NSR	JB	0 30
6 FO	NSR	JR	0 35
7 SW	NSR	JT	0 44
8 GK	AF	(AF+JR) AVD	0 47
9 SJ	NSR	JR	0 60
10 AC	AF	JR	0 80
11 RK	NSR	JR	0 83
12 HR	AF	JT	1 20
13 GB	AF	JB	1 25
14 LS	NSR	JR	1 75
15 GR	NSR	JB	2 40
16 JG	AF	JB	2 70
17 PF	NSR+ AVD	(NSR+JR) AVD+PAT with block	2 80

Abbreviations AF atrial fibrillation AVD atrioventricular dissociation *JB junctional bradycardia JR, junctional rhythm JT* junctional tachycardia NSR normal sinus rhythm and PAT paroxysmal atrial tachycardia

glucose load and liberal use of diuretics in the early preoperative period no relation to arrhythmia was noted Creatinine clearance fell in 38 out of 42 patients in this series and was still depressed in the majority after postoperative Day 2 Similar results have been noted by other workers [14,15]

Serum digoxin levels The use of prophylactic digitalization or continuation of maintenance digoxin prior to cardiac surgery [18] and the role of digoxin in postoperative arrhythmias may be re evaluated in light of the present data There were minimal changes in serum digoxin levels in 6 out of 12 patients following cardiopulmonary bypass Others,[17] attaining levels in the immediate postoperative period have demonstrated a postbypass rebound to higher levels In addition there are several factors tending to diminish digitalis requirements or to increase possibility for toxic reactions to the drugs postoperatively including hypocalcemia, hypomagnesemia [19,20] and a reduced creatinine clearance Thus the potential for postoperative digitoxic arrhythmias in patients receiving digoxin preoperatively is great Four cases of digitoxic dysrhythmia were noted in a series of 124 patients,[6] and Williams Morrow and Braunwald[5] noted three cases of probable digitoxic arrhythmia among 150 patients Although it is generally agreed that no arbitrary set of serum digoxin levels can be selected to separate toxic from nontoxic patients and there are no absolute clinical criteria to define digitalis toxicity [4] we defined two cases of digitoxicity on the basis of well established ECG criteria[21] and serum digoxin *levels in excess of 2 ng* per milliliter (Table IV) Patient JG[16] with atrial fibrillation preoperatively developed junctional bradycardia without discernible atrial activity Serum digoxin level during the arrhythmia was 2 7 ng per milliliter Patient PF[17] developed paroxysmal atrial tachycardia (PAT) with block *postoperatively with a digoxin level of 2 8* ng per milliliter In each patient, maintenance digoxin of 0 25 mg twice a day was continued until two days prior to surgery and the postbypass digoxin levels were 1 2 and 1 35 ng per milliliter, respectively

The problem of diagnosing digitoxicity arises in *those* patients with serum digoxin levels less than 2 0 during an arrhythmia which may be related to digitoxicity Morrison and Killip[17] noted that the serum digoxin levels in a group of patients who developed arrhythmia following cardiopulmonary bypass were significantly lower than in patients with ECG evidence of digitoxicity who had not undergone surgery The range of serum digoxin levels in the postbypass group was 0 9 to 1 3 ng per milliliter suggesting an increased sensitivity to digitalis glycosides in these patients Their clinical criteria for digitoxicity included supraventricular tachycardia or AV dissociation (AVD) If one also includes any junctional rhythm regardless of rate as a manifestation *of digitoxicity* then a *wide range* of serum digoxin levels is apparent in our patients with these arrhythmias (Table IV) In those patients with serum digoxin levels of 0 8 to 2 40 ng per milliliter during arrhythmia increased sensitivity to digitalis glycoside might be postulated However this clearly is not the case in those patients with lower or 0 levels of digoxin during arrhythmia Atrial fibrillation with junctional tachycardia junctional rhythm and other mani

festations of atrioventricular dissociation are well known complications of digitalis intoxication However they were present in these patients with digoxin concentrations well below recognized toxic levels In these patients another mechanism perhaps the mechanical effects of surgical trauma would have to be postulated as the etiology of arrhythmia It is apparent therefore that one cannot make a distinction between digitalis induced arrhythmia and spontaneously recurring postsurgical arrhythmia with absolute certainty in many postoperative patients

Guidelines for therapy The results of our series suggest that the incidence of postoperative digitoxicity may be reduced if maintenance digoxin is discontinued at least three days preoperatively particularly if the maintenance dose is 0 5 mg or greater If the patient receiving digoxin postoperatively develops supraventricular tachycardia junctional rhythm or atrioventricular dissociation with or without block then a serum digoxin level is indicated The result will not provide clear cut therapeutic guidelines if the serum level falls in a range of about 0 8 to 2 0 ng per milliliter In general however therapy of arrhythmias should reflect an awareness of the ambiguity between digitalis induced and spontaneously occurring arrhythmia and an attempt should be made to avoid more serious arrhythmias by continued digoxin administration The ventricular rate during supraventricular tachycardia or atrial fibrillation may be controlled with a combination of digoxin and propranolol rather than with repeated doses of digoxin alone Pronestyl may be added to the regimen Atrial fibrillation or flutter following coronary artery bypass is usually self limited and may revert to normal sinus rhythm after several days of therapy

Summary

Arrhythmias were analyzed in 50 patients undergoing cardiac surgery 27 with valve surgery 15 with coronary artery bypass (CAB) 5 with CAB and valve surgery and 3 with miscellaneous procedures. The role of electrolyte abnormalities pericarditis serum osmolarity digoxin level and the type of surgery performed was evaluated.

Thirty seven out of 50 patients (74 per cent) had a postoperative arrhythmia and a total of 78 different arrhythmias were noted Twenty six out of 27 patients with valve surgery had an arrhythmia vs six out of 15 patients with CAB ($p < 0.001$) Atrial fibrillation was the most common arrhythmia in all groups Although postoperative hypocalcemia hypomagnesemia pericarditis and wide shifts in osmolarity were common they did not correlate with arrhythmias

Seventeen patients developed postoperative arrhythmias compatible with digitalis toxicity including junctional rhythm atrioventricular dissociation or atrial tachycardia with block However the range of serum digoxin levels in these patients was zero to 2 80 ng per milliliter This suggests increased sensitivity to digitalis glycosides or the effects of surgical trauma as the etiology of arrhythmia in many patients The distinction between digitalis induced arrhythmia and spontaneously occurring arrhythmia cannot be made with certainty in most postoperative patients Therapy should reflect an awareness of the potential for postoperative digitoxicity

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The sick-sinus syndrome in Africans

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Increasing attention has been drawn in the past few years to the sick sinus syndrome a disease characterized by sinus bradycardia and syncope [1-3] Clinical reports of this disorder from developed countries suggest that the disease occurs largely in middle age and that its principal association is ischemic heart disease [3,4] However in the Cardiac Service of the Mulago Hospital Kampala Uganda we have encountered a number of young patients presenting with dizziness and syncope whose only abnormality on physical examination has been bradycardia These patients form the subject of this paper We believe that this is the first time the sick sinus syndrome has been described exclusively in Negroes Our report is also of interest because all our patients are young persons and all are below the age in which ischemic heart disease is common Moreover ischemic heart disease does not enjoy the same prominence in Uganda as it does in developed countries It is wished here therefore to draw attention to a condition which is obviously not uncommon in young persons in the tropics and whose presentation may lead to an erroneous diagnosis if the possibility of a disease of the sinoatrial node is not born in mind

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Cases studied

For this presentation we have selected patients from the Cardiac Service with persistent sinus bradycardia and symptoms referable to the cardiovascular system seen in the last five years Sinus bradycardia was defined as a sinoatrial rate of less than 60 beats per minute Patients whose bradycardia did not persist at a subsequent visit were rejected A few cases with a clinical or electrocardiographic diagnosis of paroxysmal tachycardia were also reviewed and two subjects whose basic rhythm without treatment showed a bradycardia were included in the study

A total of 15 cases were finally selected for the study All of the cases had a full cardiovascular examination and a resting electrocardiogram Eight patients had exercise tests subsequently This involved climbing two steps at the rate of about 50 steps per minute for a minimum of 150 steps An electrocardiogram was then taken in the recumbent position All patients had a postero anterior chest radiograph using standard techniques

Seven patients (Cases 1 9 10 11 13 14 and 15) had all of the following investigations hemoglobin and packed cell volume determinations random blood sugar serum cholesterol anti streptolysin O titer and serologic tests for syphilis Three others had hemoglobin and PCV determinations only

Case presentations

Representative case histories are given briefly below while the mode of presentation and the principal findings in the other eight patients are presented in Table I

Case 1 A 22 year old mechanic with a strong alcohol history had a history of irregular heart

Table 1 Clinical features in eight patients with the sick sinus syndrome

Case no.	Age	Sex	Presentation	Investigations
3	16	F	Dizziness with palpitations BP 120/80	ECG sinus bradycardia heart rate 41 beats per minute other investigations normal.
6	10	M	One episode of loss of consciousness	ECG heart rate 53 beats per minute chest radiograph normal
9	32	M	Tiredness and dizziness falls while standing at attention strong alcohol history BP 130/80	ECG heart rate 41 beats per minute PR 0 24 sec paroxysmal nodal rhythm after exercise heart rate 57 beats per minute other investigations normal
10	24	M	Palpitations and falls BP 150/110 hypertension controlled with bendrofluazide tablets	ECG heart rate 46 beats per minute after exercise 60 beats per minute
11	20	M	Palpitations for three months BP 120/80	ECG heart rate 56 beats per minute left ventricular hypertrophy other investigations normal
12	19	M	Dizziness for one month BP 130/80	ECG heart rate 44 beats per minute PR 0 21 sec
13	26	M	Episodes of rapid heart action for nine months, dizziness not associated with tachycardia BP 112/76	ECG heart rate 47 beats per minute after exercise 89 beats per minute arrhythmia not recorded other investigations normal
14	20	M	Dizziness and faintness for two years BP 110/70	ECG heart rate 58 beats per minute after exercise 73 beats per minute other investigations normal

action and of falls with loss of consciousness and shaking of the body One year earlier he had typhoid fever Physical examination apart from a heart rate of 43 beats per minute was normal Blood pressure was 140/90 The electrocardiogram showed sinus bradycardia (40 beats per minute) with voltage evidence suggestive of left ventricular hypertrophy After exercise the heart rate increased to 57 beats per minute Laboratory investigations were normal He was treated with isoprenaline tablets four per hour sublingually subsequent electrocardiograms showed no significant increase in heart rate (45 beats per minute and 48 beats per minute) He was lost to follow up after five months

Case 2 A 30 year old watchman with a strong alcohol history had attacks of palpitations and dizziness with intermittent blurring of vision for one month Physical examination revealed moderate hypertension 170/100 an audible atrial sound, and bradycardia The electrocardiogram showed sinus bradycardia (39 beats per minute) and paroxysmal coupling due to nodal beats with aberrant ventricular conduction as well as voltage evidence of left ventricular hypertrophy The chest radiograph was normal He was lost to follow up after two months

Case 4 A ten year old deaf boy had a history of tiredness and a disinclination to run with other children Blood pressure was 80/60 Bradycardia was noted on examination and confirmed on electrocardiography (43 beats per minute) The electrocardiogram also showed first degree A V block (PR,0 20 second) After exercise the heart rate was unchanged One hour after 60 mg of ephedrine orally the heart rate was 48 beats per minute He was put on ephedrine 30 mg, three times a day and two months later the heart rate was 75 beats per minute PR 0 22 second.

Case 5 An 18 year old male grass cutter with a strong alcohol history was admitted as an emergency having lost consciousness that morning while at work The total duration of this episode of loss of consciousness was five hours during which his heart rate was 45 beats per minute He later gave a history of falls preceeded by palpitations in the last four years Physical examination was normal Blood pressure was 110/70 The cerebrospinal fluid was under normal pressure and showed no abnormalities Blood sugar was 109 mg per cent Other investigations were normal The electrocardiogram apart from sinus bradycardia (44 beats per minute) was normal Subsequently he was put on Ephedrine 20

ing four times a day During the next 13 months there was no further history of falls or loss of con sciousness The sinus rate during four visits was 42 45 38 and 41 beats per minute He was lost to follow up after 13 months

Case 7 An 18 year old male presented with a history of falls and of dizziness On physical ex amination the heart rate was 44 beats per minute and the blood pressure was 120/85 The electrocardiogram revealed a sinus bradycardia (45 beats per minute) with a wandering pace maker (changing configuration of P waves and changing PR interval 0 12 to 0 20 second) asso ciated with occasional aberrant ventricular con duction There was voltage evidence of left ven tricular hypertrophy He was lost to follow up after the first visit

Case 8 A 26 year old soldier presented with a history of repeated episodes of loss of conscious ness with clonic movements tongue biting and incontinence of urine for two years He also had a history of falls not associated with a clear story of loss of consciousness or with fits There was a strong family history of similar attacks two sis ters and one brother were affected. A second brother was normal The patient had been treated for epilepsy for two years without in fluencing the frequency of the attacks On ex amination apart from a heart rate of 50 beats per minute there was no abnormality The blood pressure was 120/80 The electrocardiogram showed sinus bradycardia (45 beats per minute) and nodal escape beats with aberrant ventricular conduction Hemoglobin was 16 6 Gm per cent and white blood cells 7 600 per cubic millimeter He was put on ephedrine 200 mg four times a day Two months later he had no further history of falls or fits His heart rate was 48 beats per minute but there were no escape beats or con duction defects on the electrocardiogram

Case 15 A 29 year old male accountant with a three months history of three episodes of rapid heart action Between attacks he had episodes of dizziness and faintness with palpitations There was a history of a single episode of syncope Physical examination revealed no abnormality except bradycardia Blood pressure was 115/80 The electrocardiogram showed sinus bradycardia (46 beats per minute) but was otherwise normal The heart rate after exercise was 112 beats per minute Laboratory investigations were normal

Table II Age and sex distribution of 15 patients with sick sinus syndrome

Age in years	*Male*	*Female*
10 14	2	Nil
15 19	3	1
20 24	3	Nil
25 29	4	Nil
30 34	2	Nil
Total	14	1

Table III Clinical presentation of 15 patients with sick sinus syndrome

	No of cases	*%*
Dizziness	10	67
Palpitations	9	53 3
Syncope	8	60
Tiredness	6	40
Tachycardia	3	20
Chest pain (not angina)	3	20
Breathlessness	1	6 7

Comments on cases

The age and sex distribution of the cases in this review is presented in Table II All the patients were less than 35 years and all but two of the pa tients were less than 30 years old There was a great preponderance of males the male/female ratio being 14 to 1 The clinical presentation is tabulated in Table III Dizziness or faintness was the most frequent complaint Loss of conscious ness with falls occurred in 8 out of 15 cases and was associated with epileptiform fits in two pa tients (Cases 1 and 8) Cases 1 5 8 and 10 had more than four episodes of syncope at the time of the first hospital visit. Four other patients pre sented with intermittent headache three with episodes of chest pain not angina one (Case 4) presented with refusal to run and another pa tient (Case 3) complained of feeling frightened.

The past history yielded little information of value in any of the patients None of the patients had a history of rheumatic fever One patient had typhoid fever one year previously (Case 1) Another patient had a strong family history of falls with prolonged loss of consciousness (Case 8) The family history was negative in five other cases There was a history of consumption of

large amounts of alcohol in four patients (Cases 1 2 5 and 9) No patient had organic heart dis ease—although two patients had a raised blood pressure (Cases 2 and 10) and four other patients despite a normal blood pressure, had electrocar diograms consistent with left ventricular hy pertrophy (Cases 1 7, 11, and 13) All patients had normal chest radiographs

The patients in this review were selected because of the association of bradycardia with symptoms referable to the cardiovascular system In all of these patients the heart rate at rest ranged from 39 to 58 beats per minute (mean 45 9 beats per minute) Only three patients had a sinus rate greater than 50 beats per minute (Cases 6 11, and 14) Eight patients were sub jected to exercise The heart rate rose to above 60 beats per minute in only three of the patients. (Case 13 resting 47 exercise 89 Case 14 resting 58 exercise 73 and Case 15 resting 46, exercise 112) Of these three patients only Case 15 had a history of syncope none of the cases had abnor malities of conduction on the electrocardiogram The basis for including these three cases in the series was bradycardia with a clear history of paroxysmal tachycardia in Cases 13 and 15 and isolated persistent bradycardia in Case 14

The electrocardiograms showed nodal escape beats in three patients (Cases 2 8 and 9) Case 8 had a history of syncopal attacks Case 9 had two falls while standing at attention The electrocar diogram of Case 7 showed the presence of a wan dering pacemaker he also had a history of syn cope No patient was anemic The hemoglobin varied from 12 6 Gm per cent to 19 0 Gm per cent with a mean of 15 6 Gm per cent The mean serum cholesterol for the seven patients in whom the determination was made was 156 4 mg per cent Serologic tests for syphilis were negative for seven patients examined

Six patients were treated with ephedrine 20 to 30 mg four times a day, or isoprenaline sub lingually 100 mg every four hours (Cases 1 4 5 8, 9 and 12) Only in one case did the pulse rate subsequent to treatment, rise to above 60 beats per minute (Case 4 resting 43 one hour later 48, two months later 75 beats per minute) Four pa tients in the treated group were exercised (Cases 1 4, 5 and 9) in no case did the heart rate rise to above 60 beats per minute after exercise This would confirm the experience that these patients do not show a substantial increase in heart rate on exercise nor does the heart rate respond to therapy with sympathomimetic amines

Using the classification of Rubenstein and co workers,[4] ten patients in this series belong to their Group one (persistent unexplained sinus bradycardia), three to Group two (documented A V nodal escape beats), and two to Group three (bradycardia with well documented paroxysmal tachycardia)

Discussion

The sick sinus syndrome has become an easily recognizable clinical entity The term refers to a disorder characterized by inappropriate brady cardia not responding to exercise and associated with such symptoms as dizziness and syncope Earlier clinical descriptions of this disorder in clude those of Laslett[5] and Short [6] The latter author first pointed out that paroxysms of supra ventricular tachycardia may occur in this condi tion and may be the presenting feature Expan sion of the clinical spectrum of this disorder came with the description by Bacos Eagan and Orgain[7] of unexpected bradycardia occurring as an autosomal dominant inheritance, and the description by Jervell and Lange Nielson[8] of its association with congenital nerve deafness

Ferrer[9] has summarized the diagnostic fea tures of the sick sinus syndrome Ten of our pa tients showed persistent bradycardia and in only three patients was the heart rate greater than 50 beats per minute in two of these (age 10 years heart rate 53 age 20 years heart rate 56) the heart rate was certainly inappropriate Three other patients showed escape beats as well as bradycardia while two patients had clear histo ries of paroxysmal tachycardia We have not ex cluded from our series the three patients who showed an appreciable increase in heart rate after exercise One case (No 15) had a history of both syncope and paroxysmal tachycardia Case 13 had a history of tachycardia but no syncopal attacks It seems to us that these cases with clear cut symptoms may appropriately be in cluded in the series and that early cases may not manifest the full characteristics of the disorder the sinus node in such individuals still being capable of responding effectively to cardiovascu lar reflexes

In the clinical review of this syndrome by

Rubenstein and co workers[4] the majority of 56 patients were over the age of 40 years and there was a preponderance of females Their data also suggested a bimodal curve of distribution with an earlier peak in the third decade All our patients would fall into this earlier group The vast pre ponderance of males in our group is noteworthy although no immediate explanation for this is ap parent In their review coronary artery disease was present in 20 out of 56 patients and was thought to be the cause of bradycardia but no cause was found in 25 out of 56 Unfortunately these authors do not present the age and sex dis tribution of these 25 patients who would appear to be most closely related to our series

We are unable to offer an opinion on the etiolo gy of bradycardia in our cases All our patients were otherwise fit and only two cases had mild es sential hypertension none had ischemic heart disease and none had a cardiomyopathy Perhaps it is of interest that a history of the consumption of large amounts of alcohol was obtained in four patients (Cases 1 2 5 and 9) two of whom showed electrocardiographic evidence of ectopic pacemaker activity The toxic effects of alcohol on the myocardium are well known but we are unaware of any clearly documented evidence of selective alcohol toxicity to the conducting sys tem Moreover none of these three patients had other evidence of cardiac damage and bradycar dia is not a known feature of alcoholic cardi omyopathy

One of our patients developed sinus bradycar dia after an attack of typhoid fever although the exact relationship of the infection to the onset of bradycardia was not known Kirk and Kvorn ing[10] in a clinical review of 515 consecutive cases of sinus bradycardia had 10 cases whose brady cardia developed 10 to 20 days after the subsid ence of a febrile illness. The authors indicated that bradycardia developing during convales cence has been reported following typhoid fever diphtheria and influenza As these are all com mon tropical diseases, investigation of the an tecedent history for these conditions seem man datory Kirk and Kvorning[10] also had 229 out of 515 patients with bradycardia of previously un determined origin None of our patients had any of the disorders (colitis osteoarthritis hy pogonadism obesity rheumatic disease etc.) for which a statistical association with bradycardia seemed possible in that study It is noteworthy also that Rubenstein and co workers[4] could not determine the cause of bradycardia in about 50 per cent of their cases

Two of our patients are of particular interest. Case 8 a soldier with a history of attacks of loss of consciousness had a strong family history of episodes of loss of consciousness although we have not yet had the opportunity of examining this patient s family The other patient (Case 4) was a ten year old boy with congenital nerve deafness These two associations with the sick sinus syndrome[7 8] have been described.

It is important here to stress the bizarre clini cal presentation of some of our patients with the sick sinus syndrome Two patients in this series were thought to have psychiatric disorders on the basis of the history at presentation one was treated unsuccessfully with tofranil On the other hand, two patients had epileptiform fits and one was treated for two years for epilepsy without success a third case was admitted with an episode of prolonged loss of consciousness It is obvious that a number of persons with syncopal attacks may be mistaken for cases of epilepsy unless the significance of the associated brady cardia is appreciated

Previous publications have suggested that treatment with sympathomimetic amines or with atropine has no effect on the heart rate and may precipitate an attack of paroxysmal tachycardia We are able to confirm that no significant change in heart rate occurs following medical treatment However three of our cases with a history of syn copal attacks were treated with sympatho mimetic amines and followed up respectively for two five and thirteen months In none of these three cases did further syncope occur dur ing the period of follow up although no signifi cant change occurred in the heart rate It seems therefore that such therapy may be useful in preventing or reducing the frequency of Stokes Adams attacks In areas where the use of artificial pacemakers is impracticable sym pathomimetic drugs despite the dangers of pre cipitating a tachyarrhythmia would seem the only alternative method of attempting to reduce the frequency of syncopal attacks

The average follow up period for the patients in our series was considerably lower than that for the majority of patients attending the cardiac

service Of the eight patients who presented initially with Stokes Adams attacks, five have been lost to follow up, the other three Cases 7, 8, and 9, were seen respectively, four four, and five months ago Only Case 8 had been seen once again since the first attendance This alarming default rate may well be related to the grave prognosis of this condition in young persons, and more careful follow up of such cases in future should yield information both on the prognosis of these patients whose sinus disorder is uncomplicated by overt myocardial disease and on the effectiveness of medication in preventing syncopal attacks

Summary

Fifteen cases of the sick sinus syndrome in young Negroes are presented The etiology was unknown in all cases, organic heart disease was absent The very high default rate suggests that the prognosis may be grave This disorder is by no means uncommon in young persons in tropical countries and the dangers of a mistaken diagnosis of epilepsy or a psychiatric illness have been emphasized In the absence of an artificial pace maker it is suggested that sympathomimetic drugs while not affecting the heart rate may be useful in reducing the frequency of syncopal attacks.

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P-wave analysis in myocardial infarction pulmonary edema and embolism

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In 1964 Morris and his associates[1] proposed a new electrocardiographic measure to detect or confirm the presence of any form of left sided valvular lesion They showed that in patients with valvular heart disease abnormalities of the terminal half of the P wave in Lead V_1 (PTF V_1) correlated well with a pressure or volume over load on the left atrium Other workers[2-4] have shown that patients with acute myocardial in farction often have an abnormal PTF V_1 Chandraratna and Hodges[5] demonstrated that there was a close correlation between the magnitude of the PTF V_1 and left atrial pressure in such patients and that changes in PTF V_1 toward normal were usually accompanied by a reduction in left atrial pressure

Romhilt and Scott[6] recently showed that the PTF V_1 was abnormal in patients admitted with acute pulmonary edema with a return to normal in 72 per cent of those who recovered. It is a matter of common clinical knowledge that acute pulmonary embolism can be a difficult diagnosis to make or exclude The two most important differential diagnoses are acute pulmonary edema and acute myocardial infarction

The present study was therefore undertaken to see whether measurements of the PTF V_1 could be useful in differentiating patients in whom chest pain or dyspnea was due to predominantly left sided heart failure from those in whom the right side of the heart was mainly affected.

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Methods

The hospital medical and surgical case records were studied. Patients selected from a consecutive series were placed in one of three groups based on the following findings (1) patients meeting all the following criteria for pulmonary edema (a) evidence of ischemic hypertensive or valvular heart disease (b) typical history physical signs and radiologic picture (c) positive response to diuretic therapy (2) patients admitted with a typical history of acute myocardial infarction with confirmatory serial electrocardiograms and enzyme levels and in whom there was no clinical or radiographic evidence of pulmonary edema and (3) patients who met the following criteria for pulmonary embolism (a) chest pain and/or dyspnea (b) x ray evidence of pulmonary infarction or a positive lung scan (c) acute and transient electrocardiographic

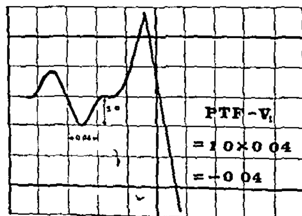


Fig 1 Method of calculation of the PTF V_1 The depth of the negative portion of the P wave in millimeters is multiplied by its duration in seconds. Since only the negative portion of the P wave is measured, the resultant PTF V_1 in millimeters-seconds is negative

service Of the eight patients who presented initially with Stokes Adams attacks, five have been lost to follow up the other three, Cases 7, 8 and 9 were seen, respectively four, four, and five months ago Only Case 8 had been seen once again since the first attendance This alarming default rate may well be related to the grave prognosis of this condition in young persons and more careful follow up of such cases in future should yield information both on the prognosis of these patients whose sinus disorder is uncomplicated by overt myocardial disease and on the effectiveness of medication in preventing syncopal attacks

Summary

Fifteen cases of the sick sinus syndrome in young Negroes are presented The etiology was unknown in all cases, organic heart disease was absent The very high default rate suggests that the prognosis may be grave This disorder is by no means uncommon in young persons in tropical countries and the dangers of a mistaken diagnosis of epilepsy or a psychiatric illness have been emphasized In the absence of an artificial pacemaker, it is suggested that sympathomimetic drugs, while not affecting the heart rate, may be useful in reducing the frequency of syncopal attacks

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than −0 02 mm sec Of the 35 patients admitted with acute myocardial infarction without any clinical or radiologic evidence of pulmonary edema four had abnormal PTF V_1 values

A comparison of PTF V_1 values between the first and last electrocardiograms taken during the patient's stay in the hospital (Fig 3) shows that in the majority of those cases with acute pulmonary edema there was a fall (though not always to normal values) concomitant with their clinical improvement Similarly the PTF V_1 also returned to normal in the four patients with acute myocardial infarction although the patient with the most negative value developed acute pulmonary edema clinically a few hours after the first electrocardiogram was recorded. By contrast in no patient with pulmonary embolism did the PTF V_1 become abnormal during his hospital stay

Discussion

It has been well established that abnormalities of the P wave are seen in patients with acute myocardial infarction[2-5] systemic hypertension,[7,8] and in valvular heart disease[1] Morris and co workers[1] concluded that abnormality of the PTF V_1 was an important electrocardiographic criterion for recognizing left heart disease

Chandraratna and Hodges[5] showed in addition that of 56 pairs of measurements in 27 patients with acute myocardial infarction only in seven patients were there changes of PTF V_1 and the estimated left atrial pressure in opposite directions

Our study confirms the findings of abnormal PTF V_1 values in patients with clinical evidence of acute pulmonary edema We also found that four of the 35 patients with acute myocardial infarction but without clinical evidence of acute pulmonary edema had abnormal values for the PTF V_1 and one of them in fact developed the typical clinical picture a few hours later

Pulmonary embolism produces elevation of right sided heart pressures and the normal PTF V_1 values obtained in these patients is compatible with normal left atrial pressures Although Oakley[9] has stated that pulmonary embolism does not cause pulmonary edema nevertheless, fluid accumulation in the lung has been reported after classic pulmonary embolism[10] Windebank and Moran[11] described 11 patients with pulmonary edema in whom subsequent investigation

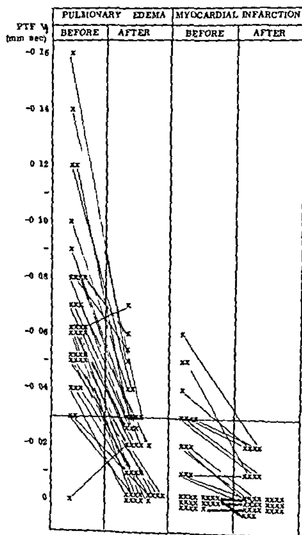


Fig 3 Change in PTF V_1 in patients with pulmonary edema or with myocardial infarction (without clinical evidence of pulmonary edema) before and after treatment

revealed the cause to be due to pulmonary embolism In four out of five of the patients in whom pulmonary wedge pressures were obtained, normal values were found while in the fifth patient the value was slightly increased. The authors suggested that the pulmonary edema may have been due to pulmonary venous hypertension as demonstrated by Daicoff Ranniger and Moulder[12] Other possible mechanisms for pulmonary edema following acute pulmonary embolism may be (1) increased capillary permeability due to vasoactive substances released from clots[13] (2) transmission of high pulmonary artery pressures to unobstructed portions of the pulmonary capillary bed, and (3) changes in surface tension produced by altered metabolism of lung

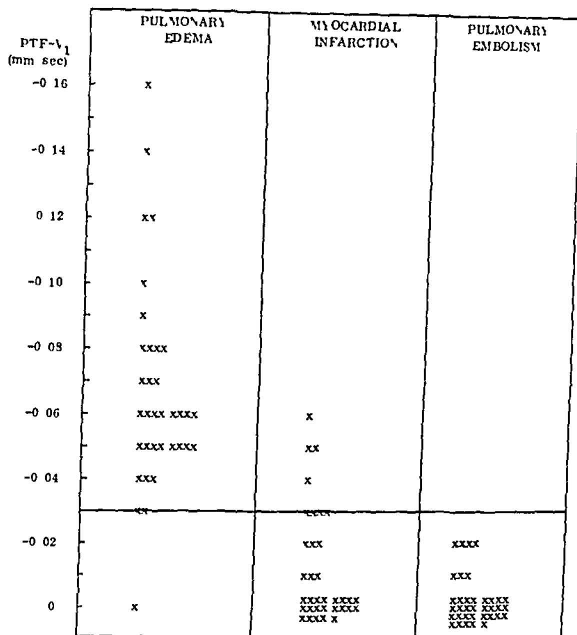


Fig 2 Values of PTF V_1 obtained on admission Thirty five patients in each group

changes of acute right ventricular strain and/or hemoptysis

Thirty five patients with pulmonary embolism who fulfilled the above criteria were found and the first 35 patients falling into Groups 1 and 2 were taken for comparison Patients who were not in sinus rhythm or whose electrocardio graphic tracings were technically unsuitable were excluded

The P terminal force in Lead V_1 (Fig 1) was measured using the method of Morris and co workers[1] on the day of admission and again from the last available tracing before discharge or death The measurements of the PTF were made from Lead V_1 of standard electrocardiograms recorded at a paper speed of 25 mm per second and a sensitivity of 1 Mv per centimeter The algebraic product of the duration (seconds) and the amplitude (millimeters) gave the P terminal force expressed as arbitary units (millimeters seconds) Only the negative portion of the P wave was measured and all positive values of the PTF V_1 were recorded as zero

A PTF V_1 of −0 03 mm sec. or a more positive value was taken as normal

Results

Fig 2 shows the PTF V_1 values in the three groups of patients It will be seen that in all but one of the patients admitted with acute pulmo nary edema the PTF V_1 was more negative than −0 03 mm sec By contrast in all patients in whom the diagnosis of acute pulmonary embo lism was made, the PTF V_1 was more positive

1915 (89)

Correlation of "critical" left coronary artery lesions with positive submaximal exercise tests in patients with chest pain

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It is well recognized that all patients with coronary artery disease do not have the same prognosis Among subgroups of patients with a higher mortality are those with unstable angina [1] those with significant three vessel disease [2] and those with certain so called critical lesions Among the latter are significant lesions of the left main coronary artery[3-5] which are generally recognized as representing a particularly high risk Other lesions purported to be associated with a particularly unfavorable prognosis are severe stenosis of the left anterior descending coronary artery proximal to the first septal perforator [6,7] and a combination of significant lesions involving both anterior descending and left circumflex arteries proximal to any major branches the so called left main equivalent (LME) lesions [8] Since coronary arteriography is useful in estimating prognosis it would be most important if there were clinically assessible factors which would predict these higher risk patients prior to angiography

Although there is still no definite proof that coronary saphenous vein bypass surgery prolongs life in patients with coronary disease it is reasonable to expect that the patients with the highest risk lesions would benefit the most It would therefore be important to identify the patients with these high risk lesions and study them with coronary arteriography

There are several observations which have been made which are pertinent in this regard Cohen Cohn and Herman[4] in reviewing their experience with significant left main coronary artery lesions reported 17 out of 20 cases (85 per cent) had 2 mm or more ST segment depression on the two step exercise test Sharma and co workers[9] reported 14 out of 17 cases (83 per cent) with 2 mm or more ST segment depression on exercise testing There appears therefore to be a high incidence of marked ST segment depression in patients with left main coronary lesions

Robb and Marks[10] in 1967 reported a direct relationship between mortality and the magnitude of ST segment depression in long term follow up of 2 224 male applicants for life insurance after the double two step exercise test The maximal period of observation was 15 years and the average was 5 6 years with at least one year of observation in every case The group with less than 1 mm ST segment depression had 2 5 times the mortality of those without any depression between 1 0 and 1 9 mm the mortality was 3 7 times the negative group and in those with 2 0 mm or more ST segment depression the mortality rose to 15 8 times that of the negative group

In 1973 Ellestad and Wan[11] reported the results of following 1 761 subjects from six months to eight years after a maximal treadmill exercise test. The eight year mortality with a

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tissue in the embolized area[14] Pulmonary edema was not a complication in any of our patients with pulmonary embolism Moreover, since the PTF V_1 is a reflection of increased left atrial pressure and left sided heart disease one would, on the basis of the above hypotheses expect it to be normal in such patients

The measurement of the PTF V_1 is simple, noninvasive and repeatable and our results show that it may be of value in differentiating acute dyspnea due to left ventricular failure from acute dyspnea secondary to pulmonary embolism In patients in whom the differential diagnosis rests between acute myocardial infarction and acute pulmonary embolism as the cause of their chest pain it is of occasional value in alerting the physician to subclinical left ventricular failure secondary to myocardial infarction particularly if serial changes show a return to normal values

Summary

In a retrospective study the P terminal force in Lead V_1 (PTF V_1) was measured in three groups each of 35 patients with the respective diagnoses of acute myocardial infarction without pulmonary edema acute pulmonary embolism, and acute pulmonary edema In all but one of the patients with acute pulmonary edema a highly negative PTF V_1 value was obtained whereas by contrast all the patients with pulmonary embolism had normal PTF V_1 values Four of the patients with acute myocardial infarction had abnormal PTF V_1 values, although at the time there was no clinical or radiologic evidence of pulmonary edema However one of these patients did develop acute pulmonary edema a few hours later

Measurement of the PTF V_1 is a simple noninvasive test that may, therefore be useful in separating patients with acute pulmonary embolism from those with acute or impending pulmonary edema

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Correlation of 'critical' left coronary artery lesions with positive submaximal exercise tests in patients with chest pain

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Although there is still no definite proof that coronary saphenous vein bypass surgery prolongs life in patients with coronary disease it is reasonable to expect that the patients with the highest risk lesions would benefit the most It would therefore be important to identify the patients with these 'high risk lesions and study them with coronary arteriography

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Table I Age and sex

	No	M/F	Age range (years)	Mean age (years)
Group I	45	39/6	23 63	52 1
Group II	31	28/3	32 64	44 4
Group III	30	24/6	29 65	41 9

negative exercise test was 2 per cent, with ST segment depression between 0 5 mm and 1 4 mm it was 12 per cent and when ST segment depression was 1 5 mm or more the mortality was 22 per cent The incidence of development of myocardial infarction was related in a similar way to the degree of ST segment depression With a negative test the eight year incidence of myocardial infarction was 2 per cent, with ST segment depression 0 5 to 1 4 mm it was 9 per cent, and with 1 5 mm or greater it was 31 per cent. It is therefore apparent that the incidence of coronary events and mortality is strikingly increased with a markedly positive stress test.

The present study was designed to evaluate the relationship of the degree of ST segment depression after a submaximal treadmill exercise test to the extent of coronary arterial disease and to the incidence of the following so called critical lesions' left main coronary lesions, left main equivalent lesions and very proximal severe, left anterior descending lesions

Methods

All patients with coronary disease by arteriography in whom both coronary arteriogram and an adequate submaximal treadmill test was available at Walter Reed Army Medical Center were included in the study There were 106 such patients All patients had been studied for chest pain Patients with congenital coronary arterial anomalies valvular heart disease and idiopathic hypertrophic subaortic stenosis were excluded

The treadmill test at Walter Reed Army Medical Center is done on patients off digitalis for at least one week and other medications for at least 48 hours The treadmill test is similar to that described by Kattus Alvaro and MacAlpin[12] and is done according to the following protocol

The patient is started at 1 0 mile per hour at a 10 per cent grade The speed is increased every three minutes by 0 5 mile per hour until the speed of four miles per hour is achieved A modified V_5 chest lead is monitored throughout the exercise After exercise, Leads V_6 V_5 V_4 aV_F, aV_L II, and I are recorded immediately and every two minutes until ten minutes after exercise or until the electrocardiogram (ECG) has returned to baseline The test is complete when (1) 85 per cent of maximal heart rate for age is achieved (2) the ST segments have become more than 2 mm depressed (3) the patient develops angina, shortness of breath, or fatigue which has increased in severity to the point where the patient says that he must stop or (4) significant ventricular arrhythmia begins or worsens

Coronary arteriography was performed by the Judkin s technique[13] with selective angiography done in multiple degrees of right and left obliquity and recorded on 35 mm cine film at 60 frames per second The coronary arteriograms were evaluated by at least two of the authors and graded according to the per cent of diameter narrowing of the lumen The evaluation of angiograms exercise tests and degree of angina were made by independent observers The coronary arteriograms were evaluated, for the most part without knowledge of the results of the exercise test In some cases this was not possible because either the patient or the arteriogram was recognized by the evaluator An estimate was made of the anatomic feasibility of saphenous vein bypass grafting in each instance This did not include an estimation of ventricular function or other factors such as pulmonary disease that might effect a decision to recommend surgery

The patients were then divided into three groups according to the degree of ST segment depression Group I ST segment depression 2 mm or more Group II ST segment depression 1 0 to 1 9 mm and Group III, ST segment depression 0 to 0 9 mm The ST segment depression was measured as a departure from control ST segment and was flat or downsloping with a duration of 0 08 second or longer

The angiograms were then evaluated for the presence of critical lesions as defined (1) 75 per cent or greater narrowing of left main coronary artery (LMCA) (2) 75 per cent or greater narrowing of left anterior descending coronary artery and 75 per cent or greater narrowing of left circumflex coronary artery both proximal to any major branches the so called left main equivalent lesion (LME) and (3) 90 per cent or greater

Table II Incidence of critical lesions according to degree of ST segment depression

	No.	NCL	Critical lesions			Total critical lesions
			LMCA	MLE	LAD	
Group I (ST depression 2 mm or more)	45	11	11 (24 4%)	13 (28 9%)†	10 (22 2%)	34 (75 5%)‡
Group II (ST depression 1 0 1 9 mm)	31	21	0	4 (12 9%)	6 (19 3%)	10 (32 2%)§
Group III (ST depression 0 0 9 mm)	30	28	0	0	2 (6 7%)	2 (6 7%)

NCL = noncritical lesions.
Group I vs. Group II and III p < 0 01
†Group I vs Group III p < 0 01
‡Group I vs. Group III p < 0 001
§Group II vs Group III p < 0 02

Table III Incidence of vessels with 75 per cent or greater obstruction according to degree of ST segment depression

	No	1 vessel	2 vessel	3 vessel
Group I (ST depression 2 mm or more)	45	8 (17 8%)	14 (31 1%)	23 (51 1%)‡
Group II (ST depression 1 0 1 9 mm)	31	9 (29 0%)	16 (51 6%)	5 (16 1%)
Group III (ST depression 0 0 9 mm)	30†	17 (56 7%)§	8 (26 6%)	3 (10 0%)¶

Includes 1 patient with < 75 per cent obstructive lesions
†Includes 2 patients with < 75 per cent obstructive lesions
‡Group I vs Group III p < 0 0)
§Group III vs Group I p < 0 001
¶ Group III vs. Group I p < 0 001

narrowing of left anterior descending coronary artery proximal to the first major branches (LAD)

The severity of coronary pathology by the number of vessels involved and by the presence of critical lesions was then evaluated in the three groups of patients categorized by the magnitude of ST segment depression

The patients records were evaluated and the severity of angina pectoris classified arbitrarily as mild moderate moderately severe and severe There was in addition a group of patients who could not be so classified and they were grouped together as unknown For statistical purposes these were evaluated by combining the mild and moderate groups and the moderately severe and severe groups.

Statistically the results were evaluated by the chi square test employing Yates correction for continuity wherever individual cell frequencies were small [14]

Results

There were 106 patients in the study There were 45 patients in Group I 31 patients in Group II and 30 patients in Group III Table I shows the age and sex distribution The mean age tended to be older as the magnitude of ST segment depression became greater

Table II shows the incidence of critical lesions in each of the ST segment depression groups In patients with 2 mm or more ST segment depression (Group I) 75 per cent had critical lesions 24 4 per cent had LMCA lesions 28 9 per cent had MLE lesions and 22 2 per cent had LAD lesions

In this study all patients with LMCA lesions had 2 mm or more ST segment depression Of the patients with MLE lesions there were significantly more patients ($p < 0\ 01$) in Group I than in Group III Although the number of left anterior descending lesions is too small to reach significance at the $p < 0\ 05$ level there is certainly a trend toward more left anterior descending lesions as the depth of ST segment depression increases

Of the total number of patients with critical lesions 34 out of 46 or 73 9 per cent were in Group I and 44 out of 46 or 95 7 per cent were in Groups I and II Only two patients out of 46 with critical lesions had a negative stress test defined as less than 1 mm of ST segment depression and they both had 90 per cent or greater proximal LAD disease

Table IV Severity of angina pectoris vs angiographic lesions and degree of ST segment depression

	Mild moderate	*Moderate Severe Severe*	*Unknown*	*Total*
Angiographic lesions				
Critical	18	25	3	46
Noncritical	28	18	14	60
ST-depression				
Group I	18	22	5	45
Group II	13	14	4	31
Group III	15	7	8	30

Table V Operability

Group I	82 4%
Group II	87 0%
Group III	86 6%

Table III lists the incidence of 75 per cent or greater obstruction in one two and three vessels in each of the ST segment groups There were significantly more patients with one vessel dis ease ($p < 0\ 001$) in Group III than in Groups I and II In our institution patients with less than 1 mm of ST segment depression (Group III) are considered to have a negative stress test There were significantly more ($p < 0\ 01$) patients with three vessel disease in Group I than in Group III

In patients with 2 mm or more ST segment de pression 51 1 per cent had three vessel disease and 82 2 per cent had two or three vessel dis ease When the ST segment depression was be tween 1 and 1 9 mm 67 7 per cent had two or three vessel disease and in patients with less than 1 mm of ST segment depression 36 7 per cent had two or three vessel disease Of all pa tients with two or three vessel disease 37 out of 69 or 53 6 per cent had ST segment depression equal to or greater than 2 mm and 58 out of 69 or 84 1 per cent had ST segment depression equal to or greater than 1 mm Of the 45 patients with 2 mm or more ST segment depression only two patients had severe stenosis of the right coro nary artery without lesions in the left coronary system When correlations with severity and fre quency of angina were attempted except for the fact that there were no mild angina patients with LMCA lesions it was not possible to distinguish the patients with from those without critical le sions (Table IV) It was also not possible to corre late the severity of anginal symptoms with the magnitude of ST segment depression except for the relative rarity of mild angina in the presence of severe ST segment depression (Table IV)

Table V lists the per cent operability according to each ST segment group as estimated by two of the authors on the basis of anatomic feasibility only Over 80 per cent of the patients in each group were amenable anatomically to bypass surgery

Discussion

It is important to realize that all the patients in this study underwent coronary arteriography because of chest pain all had a coronary ar teriogram and an adequate submaximal tread mill test available and only patients who had coronary artery disease by arteriography were included

Therefore not all left main coronary artery le sions seen at Walter Reed Army Medical Center are included in this study Patients having severe angina at rest were not subjected to treadmill testing and therefore would not be included It also is possible that not all patients with 2 mm of ST segment depression on treadmill testing have this high incidence of LMCA lesions or other critical lesions ' as defined, since we do not usually study asymptomatic patients with abnor mal treadmill tests It is known that there are a group of patients with markedly abnormal tread mill tests who have normal coronary arteries by arteriography [15] This type of patient also is not included in this study

The reported poor prognosis attributed to the 'critical ' lesions as defined is also not to be ex amined in this study Thus it is not certain that the LME lesions as defined in this study have the same apparent poor prognosis as LMCA lesions The serious prognosis in very proximal left an terior descending lesions is also not totally ac cepted [16]

It cannot be stated that all patients with criti cal lesions are at such high risk that they will all necessarily benefit from saphenous vein bypass surgery since there is very little evidence, except for, perhaps the LMCA lesions [17] that such sur gery either prolongs life or prevents myocardial infarction

It would appear reasonable to assume that sur

gery would be most helpful in those patients at highest risk From the anatomic standpoint, over 80 per cent of our patients were operable The number of patients submitted to surgery would obviously be lower when other important clinical factors such as ventricular function and the presence of other systemic disease such as pulmonary and renal disease are taken into account

What this study does indicate is that in patients with angina and 2 mm. or more ST segment depression on exercise testing who have coronary arterial disease by angiography a large percentage have critical lesions as defined. It is also apparent that with an adequate submaximal treadmill stress test a negative result as defined as less than 1 mm. of ST segment depression will fail to identify less than 5 per cent of all patients with such critical lesions

ST segment depression or exercise testing is the electrophysiologic clinically obtainable manifestation of myocardial ischemia as it exists under the circumstances of the imposed work load It is reasonable to suppose that the degree of ST segment depression correlates with the volume of myocardium involved and the degree to which this myocardium is rendered ischemic with the exercise The increased mortality with these critical lesions is most likely related to the large volume of myocardium compromised by these lesions The good correlation of arteriographically observed critical lesions with marked depression of the ST segment appears to support this supposition

In patients with medically controllable angina who have less than 1 mm. of ST segment depression with an *adequate* submaximal exercise test there is less than a 5 per cent chance of missing one of the so-called critical lesions From this data we conclude that coronary arteriography is not necessary in this group of patients

Summary

This study correlates the anatomic pathologic coronary anatomy found by arteriography in each of three groups of symptomatic patients all with coronary artery disease divided according to the magnitude of ST segment depression after an adequate submaximal treadmill exercise test. Group I consists of 45 patients with ST segment depression of 2 mm or more Group II of 31 patients with ST segment depression between 1 0 and 1 9 mm. and Group III 30 patients with 0 to 0 9 mm ST segment depression Seventy five per cent of the patients in Group I had critical lesions defined as (1) 75 per cent or greater narrowing of left main coronary artery (LMCA) (2) 75 per cent or greater obstructive left anterior descending and left circumflex coronary artery both proximal to any major branching the so called left main equivalent (LME) lesions and (3) 90 per cent or more obstruction of the left anterior descending coronary proximal to any major branches Of patients in Group I 24 per cent had LMCA lesions 29 per cent had LME lesions and 22 per cent had LAD lesions Eight two per cent of Group I patients had two- or three vessel disease All patients with LMCA lesions had 2 mm. or more ST segment depression Over 95 per cent of patients with critical lesions had a positive submaximal treadmill test of 1 mm. or more ST segment depression Since the chance of missing one of these so called critical lesions is less than 5 per cent in the presence of an adequate submaximal treadmill test that shows less than 1 mm of ST segment depression it is concluded that in such patients with medically controllable angina coronary arteriography is not necessary

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A His bundle electrocardiographic analysis of cardiac conduction in the pediatric and adolescent patient

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During the past five years increasing data have been obtained concerning arrhythmias and A V conduction using the techniques of recording His bundle electrograms The catheterization techniques were described by Scherlag and co workers first for the dog[1] and soon afterward for human adults[2] More recently preliminary reports on the feasibility and usefulness of these techniques in studying A V conduction in children were first presented by Brodsky and co workers[3] and by Cohen Samet and Yeh[4] in 1970 Since then several additional papers reporting electrophysiologic data obtained from His bundle recordings in pediatric patients[5-9] have been published The purpose of this report is to present a His bundle electrocardiographic analysis of A V conduction in a series of children who had no demonstrable abnormality at cardiac catheterization and to contrast this with a group of children who had documented congenital and acquired heart disease with or without apparent disturbances in A V conduction by standard surface electrocardiograms

Methods

A total of 30 patients were studied. At the time of diagnostic cardiac catheterization 29 patients (aged 3 to 18 years) were also studied with recordings of right atrial and His bundle electrograms His bundle recordings were obtained in the other patient with congenital complete heart block at the time of therapeutic insertion of a temporary pacemaker The patients were studied in the postabsorptive state and under light sedation using a barbiturate with or without small doses of meperidine A separate informed consent form was obtained for the electrophysiologic study Diagnostic hemodynamic data were obtained prior to the electrophysiologic study and where indicated, diagnostic angiography was performed immediately following the electrophysiologic study The initial No 5 French bipolar electrode catheter with tip electrode and a second electrode 1 cm proximal to the tip was introduced either percutaneously into the right femoral vein using a catheter introducer or via the right saphenous vein using the technique of surgical cutdown A second bipolar electrode catheter (No 4 or 5 French) was then introduced either via a previously exposed antecubital vein or percutaneously using the left femoral vein The catheter sites were dependent upon which were most suitable for obtaining necessary diagnostic cardiac catheterization data In a few cases where the right saphenous vein was used and was of sufficient size both electrode catheters were introduced via this vein

The catheters were advanced under fluoroscopic control and intracardiac electrographic monitoring to right atrial positions and the catheter was positioned to record the His bundle electrogram as previously described[10] The electrode catheters were connected to a multichannel photographic recorder with connecting

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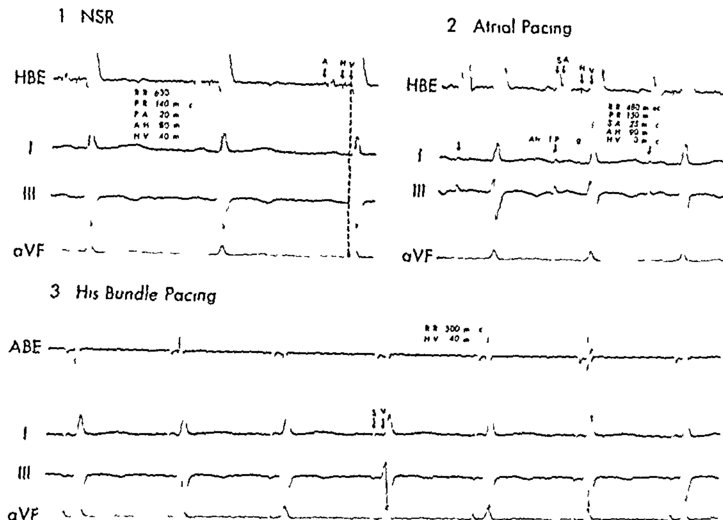


Fig 1 Recordings from patient No 3 a 6 year old female with no evidence of heart disease Panel 1 during nor mal sinus rhythm (NSR) illustrates the His bundle electrograms (HBE) with atrial (A) His bundle (H) and ven *tricular (V) deflections Simultaneous surface ECG leads (I III and* aV_F*) are displayed with the dotted line (---)* timing the earliest evidence of ventricular activity Intervals are measured to the nearest 5 msec and the inter vals are explained in the text Panel 2 during atrial pacing uses the same symbols except for the atrial pacing stimulus (S) Panel 3 during His bundle pacing illustrates the interval between the pacing stimulus and the ven tricular electrogram was identical to the H to V time during NSR and atrial pacing The solid vertical lines are at one second intervals

cables and three simultaneous surface elec trocardiogram (ECG) leads were displayed and recorded from a single set of ECG leads using suitable patching cables. The bipolar electro grams were recorded between frequency lim its of 40 and 200 cycles per second and the sur face ECG leads between frequencies of 0 and 200 cycles per second

A V conduction intervals were measured using the bipolar electrograms recorded from the cath eter positioned to record the His bundle elec trograms and the three simultaneously recorded surface ECG leads (I, aV_F and V_1 or I, III, and aV_F) Pacing from the right atrial and the His bundle catheter electrodes was performed to evaluate the A V conduction system and to vali date the His bundle electrogram in all cases

Since the valid measurements of A H and H V intervals were dependent upon the recognition of the His deflection we felt it necessary to validate the suspected His deflection by the technique of His bundle pacing [10] The catheter positioned to record the His bundle deflection was therefore, used to pace this area The His deflection was considered valid when pacing from this area resulted in a stimulus to ventricle interval identi cal to the control H V interval and produced no change in QRS contour on the three surface ECG leads as compared to control during sinus rhythm or to atrial pacing at an R R interval comparable to that during His bundle pacing This elec trophysiologic portion of the diagnostic cathe terization study added about 15 minutes to the total catheterization time No arrhythmias were induced and no complications were observed during or after the study

Results

Control A V conduction intervals Fig 1 shows typical recording from patient No 3 (see Table I) a six year old normal boy Panel 1 shows the His bundle electrograms and surface ECG leads I III and aV_F Three distinct deflections can be identified in the His bundle recordings. The first one labeled A represents the bipolar electrogram of low right atrium near the A V node The second deflection is the His bundle electrogram (H) The third deflection (V) is the ventricular activation recorded from the His bundle electrodes Thus the P R interval during normal sinus rhythm which represents the total A V conduction time can be subdivided into three segments The P A interval may be considered as a rough approximation of the intra atrial conduction time The A H interval indicates the A V nodal conduction time The H V interval indicates intraventricular conduction time At a rate of about 95 per minute the P R interval was 140 msec. The values for P A A H and H V conduction times are illustrated. Panel 2 shows a typical response to atrial pacing The A H interval or the A V nodal conduction delay increased from the control value of 80 to 90 msec. but the intraventricular conduction time remained essentially unchanged Validation of the His bundle electrogram was performed by pacing through the same bipolar electrodes used for His bundle recording Panel 3 shows that with His bundle pacing the QRS contours were the same as during normal sinus rhythm (NSR) and that the interval between the pacing spike and the beginning of QRS is the same as the H V interval recorded during spontaneous conducted beats

The age sex resting heart rate and P R interval with its components for the 14 patients with no demonstrable hemodynamic abnormality by cardiac catheterization are shown in Table IA These 14 patients underwent cardiac catheterization for evaluation of a cardiac murmur Intracardiac shunts were ruled out by appropriate double draw indicator dilution curves. If the shunt test were negative and no pulmonary out flow gradient demonstrated a percutaneous retrograde left heart catheterization was done with aortic root cineangiography to rule out a bicuspid aortic valve These patients constitute our control group with a mean age of 10 years and a mean resting heart rate of 91 per minute The mean P R interval was 145 msec. with major A V conduction delay localized to the A V node (90 msec) The mean intra atrial (P A) and intraventricular (H V) conduction times were 16 and 39 msec. respectively

Table II shows the same information for patients Nos 15 through 30 who were found to have heart diseases The last column on the right shows the diagnosis for each patient in this group Thirteen patients had congenital heart disease and one each had previous myocarditis (patient No 19) rheumatic heart disease (patient No 26) and Friedreich s ataxia (patient No 30) The normal patient group and those with heart disease were quite comparable with respect to age (10 and 11 years respectively) and their control heart rates were identical *The mean P R in*terval was 163 msec for this group of patients This is 18 msec. longer than the control group with the same mean resting heart rate This difference in P R interval was mainly due to the

Table I Control intervals (in milliseconds) for normal children

Patient No.	*Age and sex*		*Rate*	*P R*	*P A*	*A H*	*H V*
1	6	F	105	205	20	140	45
2	6	M	100	120	25	65	30
3	6	F	95	140	10	90	40
4	7	F	125	135	25	75	35
5	8	F	100	145	0	105	40
6	8	F	125	115	10	70	35
7	10	F	70	140	10	90	40
8	10	M	95	155	20	100	35
9	11	M	100	150	25	85	40
10	12	F	80	155	40	70	45
11	13	F	75	135	0	95	40
12	13	M	75	175	20	110	45
13	14	F	70	125	5	80	40
14	15	M	60	135	20	80	35
Mean	10		91	145	16	90	39
S D	3 1		20	23 2	11 2	20	4 5
S E.	0 8		5	6 2	3	5	1 2

Control intervals (to nearest 5 msec) are illustrated for 14 normal children (Table I) and 16 patients with heart diseases (Table II) Age (years) and sex are listed, and control heart rates (beats per minute) are followed by conduction times (milliseconds) with mean standard deviation (S D) and standard error (SE) illustrated immediately below the two groups of patients

( ) Asterisks indicate values two standard deviations outs de the mean of the control group

(×) is from patient No 25 who had congenital heart block and a control h art rate of 42 per minute and a narrow QRS His heart rate was not included in calculating the mean of this group.

(+) indicates control values from patient No 30 obtained during a period of n rmal sinus rhythm

The various diagnoses of patients in Table II (DX) included pulmonary stenosis (PS) single ventricle (SV) tetralogy of Fallot (TF) myocardiopathy (Myo) ventricular septal defect (VSD) complete heart block (CHB) rheumatic heart disease (RHD) m tral insufficiency (MI) aortic insufficiency (AI) tricuspid insufficiency (TI) patent d ctus arteriosus (PDA) and Friedreich s ataxia (FA)

Table II Control intervals (in milliseconds) children with heart diseases

Patient No	*Age and sex*		*Rate*	*P R*	*P A*	*A H*	*H V*	*Dx*
15	3	F	95	130	20	80	30	PS
16	4	F	90	145	20	80	45	SV
17	7	F	85	150	0	110	40	PS
18	8	M	90	140	15	90	35	TF
19	8	M	95	200	15	145	40	Myo
20	8	M	95	125	0	85	40	PS
21	10	M	95	165	10	110	45	TF
22	10	M	90	135	15	85	35	PS
23	12	M	95	120	0	85	35	VSD
24	12	M	95	215	30	140	45	Postoperative coarctation
25	12	M	42x	—	—	—	40	Congenital CHB
26	13	F	100	170	20	100	50	RHD (MI AI TI)
27	16	M	95	175	20	110	45	AI
28	17	M	80	230*	70*	120	45	A V canal
29	17	F	100	185	40	100	45	VSD PDA
30	18	F	60+	160+	5+	110+	45+	FA
Mean	11		91	163	19	103	40	
S D	4 4		10	33	15 2	21 0	4 8	
S E	1 1		2 6	8 6	4	5 2	1 2	

For abbreviations see Table I

difference in A H interval or the A V nodal conduction time The mean intra atrial and intra ventricular conduction times were not significantly different The asterisks indicate values two standard deviations outside the mean of the control group Patient No 30 had Friedreich s ataxia These values were obtained during normal sinus rhythm She had runs of atrial arrhythmias and A V conduction disturbances which will be shown later

Fig 2 shows the mean values and standard deviations of the A H and H V intervals for the control children and children with heart diseases The resting heart rates were identical for both groups The A H interval was 13 msec longer in the group with heart disease but the difference was not statistically significant As expected the A H time increased with pacing rate for both groups In contrast to the A H interval the H V interval was essentially the same for both groups at rest and during pacing

The following will illustrate unique data obtained from our patients

The P A interval The P A interval is measured from the earliest onset of the P wave in the surface ECG to the beginning of atrial activity on the His bundle recordings It is a function of intra atrial conduction and varied from 0 to 40 msec in the normal group and 0 to 70 msec in the group with heart disease Patients Nos 10, 28 and 29 had P A intervals of 40 70, and 40 msec respectively These values were significantly prolonged Patient No 28 had large intracardiac shunt at the atrial level with markedly enlarged atria to account for his P A prolongation However, patient No 10 was a 12 year old male with an ejection murmur, but no demonstrable heart disease at cardiac catheterization The etiology of his P A prolongation is not known Fig 3 illustrates the record obtained from patient No 28 a 17 year old white male with A V canal and markedly enlarged atria Note that the first degree A V block was due to intra atrial conduction delay This patient s A V nodal and intraventricular conduction times were within normal limits

The A H interval The A H interval is a measure of A V nodal transmission time from the onset of the A wave in bipolar recording to the initial deflection of the His bundle spike and varied from 65 to 140 msec in the normal group and 80 to 145 msec in the group with heart disease It can be seen that only patient No 1 in the hemodynamically normal group had a prolonged A H time which was responsible for the first degree A V block of undetermined etiology This is contrasted with the abnormal group where two patients (Nos 19 and 24) had an A H time exceeding 130 msec Fig 4 shows recordings obtained from patient No 19 an eight year old white male with myocardiopathy and first degree A V block The P R interval was 200 msec at a

rate of 90 per minute (upper limits of normal in this age group is 180 msec) The intra atrial con duction time was 20 msec which is normal The A H time was 140 msec and the H V time was 40 msec In this case the first degree A V block was due to A V nodal conduction delay

The H V interval The H V interval represents the intraventricular conduction time The intra ventricular conduction time was not prolonged in a patient with complete right bundle branch block (patient No 19 Fig 4) It may seem paradoxical thus to find that in patient No 26 a 13 year old female with severe rheumatic heart disease a normal P R interval was found with a prolonged intraventricular conduction time (Fig 5) Thus the His bundle electrograms revealed the abnormal intraventricular conduction delay which could not be detected by the surface ECG It is also worth noting that the H V interval was normal in a 12 year old male (patient No 25) with congenital heart block a narrow QRS and a heart rate of 42 per minute (Fig 6)

Combined conduction delays Conduction delays occurring in more than one of the three components (intra atrial A V nodal and intra ventricular) of the A V conduction system were found in a patient with Friedreich s ataxia Fig 7 was recorded from patient No 30 while she was having runs of atrial arrhythmias The upper panel displays Lead aV_F from a routine ECG Markedly abnormal atrial activity is noted with marked spontaneous variation in P P intervals changes in P wave contour and P waves which should have been but were not conducted to the ventricle The lower panel is a control recording of the His bundle electrogram and three simulta neous surface leads (I aV_F, and V_1) This discloses beat to beat striking variation in A A time with not only significant associated variation in A H times, but also changes in H V time from as little as 30 msec. to as prolonged as an abnormal H V time of 60 msec. Also note the deflections labeled A which occur randomly in the His bundle electrogram and probably represent aberrant or ectopic atrial activities or local re entries which are not seen in the surface ECG

Wenckebach phenomenon in the A V conduc tion system. The sites of Wenckebach type A V block induced by atrial pacing have also been localized with the use of His bundle recording techniques Fig 8 shows records obtained from a normal 14 year old female (No 13) with a resting heart rate of 82 per minute and normal A V con

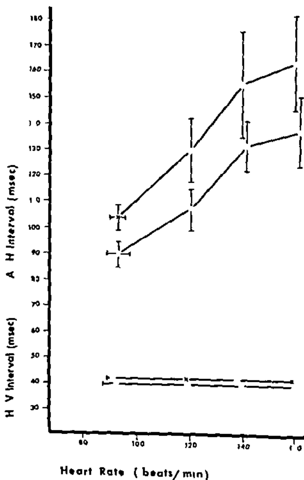


Fig 2 Mean values (milliseconds) for atrium to-His bundle (A H) and His bundle to-ventricle (H V) intervals are illus trated on the ordinate and heart rate (beats per minute) on the abscissa The values for patients with no heart disease ( ) are compared with those patients with heart disease (x) Ver tical bars represent one standard deviation from the mean values

duction intervals With atrial pacing the A H time increased (middle panel) and she developed three to two Wenckebach at a pacing rate of 170 per minute (lower panel) The P P or the A A in terval was constant at 350 msec The A H time increased from 120 to 215 msec and the third atrial electrogram was not followed by an H deflection indicating the block was proximal to the His bundle probably in the A V node

We have also localized the Wenckebach type A V block occurring in the His-Purkinje system Fig 9 shows this finding Panel 1 shows the con trol recordings of patient No 19 an 8 year old male with myocarditis of unknown etiology His cardiac catheterization however, revealed no ob vious abnormalities other than in A V conduc tion He had a prolonged P R interval which was



Fig 3 Control data from patient No 28 a 17 year old male with A V canal defect Abbreviations are identical to Fig 1 and dotted lines (---) indicate the earliest discernible atrial and ventricular activity from the simultaneously recorded leads

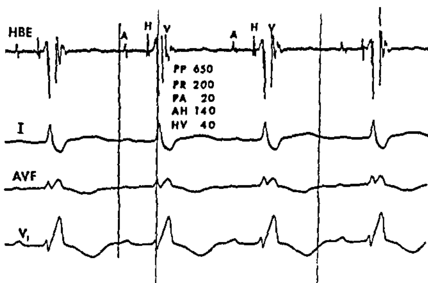


Fig 4 Control recordings from patient No 19 an 8 year old male with myocardiopathy during NSR with first degree A V block and complete right bundle branch block pattern

due to the prolonged A H time Note that this patient had right bundle branch block but his intraventricular conduction time was not prolonged. The H V interval was 40 msec which was normal Panel 2 verified the His bundle deflection by His bundle pacing Panel 3 shows a probable right bundle electrogram with a right bundle to V time of 25 msec Panel 4 was recorded during atrial pacing at a pacing stimulus interval or S S of 410 msec (146 per minute) The first beat of this panel revealed NSR with a normal QRS contour Note that there was no change in A H or H V here as compared to panel 1 The second QRS was not preceded by a His bundle electrogram and therefore was a premature ventricular contraction (PVC) rather than a supraventricular premature depolarization with aberrant conduction Atrial pacing was then started and there was a progressive prolongation of the A H interval from the first paced beat value of 145 to 280 msec in the fifth paced beat The H V interval also increased from 40 to 70 160 and 260 msec,

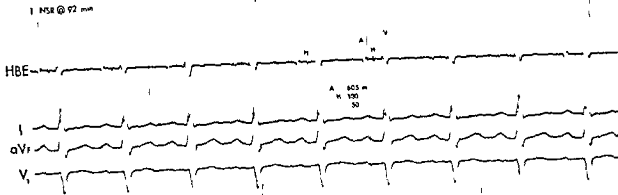


Fig 5 Control recordings from patient No 26 a 13 year-old female with severe rheumatic heart disease Note the prolonged H V time of 50 msec as illustrated by the asterisk ( )

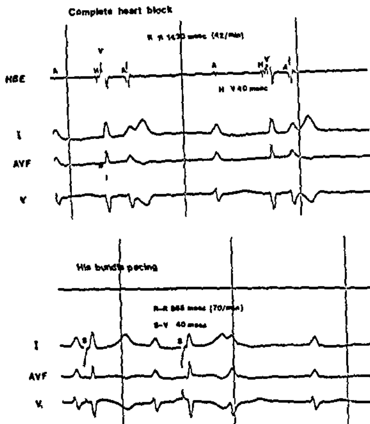


Fig 6 Control recordings (upper panel) and recordings during His bundle pacing (lower panel) are illustrated from patient No. 25 a 12 year-old male with congenital complete heart block The QRS is narrow and does not change in contour during His bundle pacing with similar intervals for H V time in the upper panel as compared to the stimulus to-V time (S-V) during His bundle pacing

and then the fifth paced beat was not conducted to the ventricle The A to V time progressively increased from 185 to 290 395 and 510 msec. and then A V block occurred. This represents 5 4 Wenckebach in the ventricular conduction system distal to the His bundle Thus Wenckebach phenomenon can occur in the specialized conduction system of the ventricle

Discussion

We have demonstrated that it is practical to study A V conduction in children by the use of

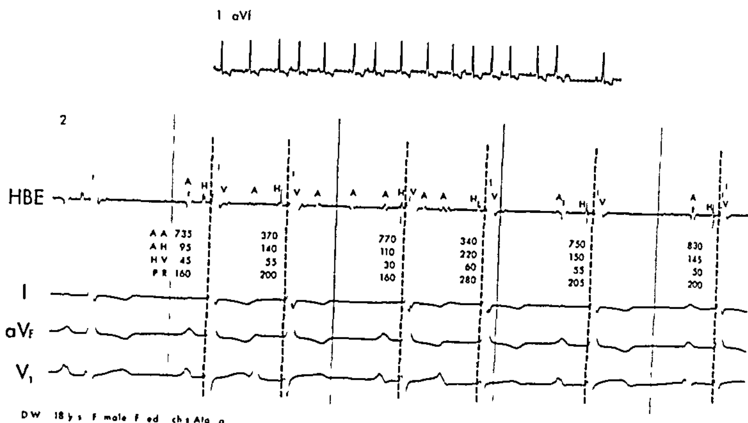


Fig 7 Control recordings from patient No 30 an 18 year old female with Friedreich s ataxia are illustrated during a period of atrial arrhythmia Panel 1 is Lead aV_F at a paper speed of 25 mm per second. Panel 2 illustrates on the His bundle electrogram striking variations in A H and H V intervals as well as deflections labeled A which represent atrial activity not seen on the surface ECG leads

His bundle recording techniques New and useful information can be obtained from intracardiac recordings which will permit more precise analysis of cardiac arrhythmias and conduction disturbances.

We have provided for the first time information on the intra atrial conduction time in children In a few patients the apparent P A time was reported as O msec This could result from one of the following three possibilities (1) the earliest P wave activity in the surface ECG might not have recorded (2) atrial activation was not reflected simultaneously in the surface ECG i e atrial depolarization might have proceeded before any visible P wave was recorded and (3) the pacemaking cell was not localized in the upper area of the sino atrial node

The control A V nodal conduction time or the A H interval was longer in our patients than those patients reported by Roberts and Olley [7] Nevertheless both sets of data are within one standard deviation of each other We were unable to confirm the report by the same authors that the intraventricular conduction time (H V interval) increased significantly with increasing age of the children We have, however, confirmed previous findings of Kelly and co workers[8] and Rosen and co workers[5] that the H V time was normal in children with congenital heart block and narrow QRS

In addition to presenting data showing localization of sites of various degrees of heart blocks with the use of His bundle recording techniques the same recording techniques can be used to localize the pacemaking site therefore allowing differentiation of a supraventricular from ectopic ventricular depolarization More important His bundle recordings have allowed us to have a better and more complete understanding of the cardiac electrophysiologic status of the patient as demonstrated in the case of patient No 26 with rheumatic heart disease and in the patient with Friedreich s ataxia In the former the P R interval as recorded in surface ECG was completely normal but His bundle recordings revealed the abnormal conduction delay in the ventricle (Fig 5) In the latter His bundle recordings revealed frequent ectopic atrial activities or

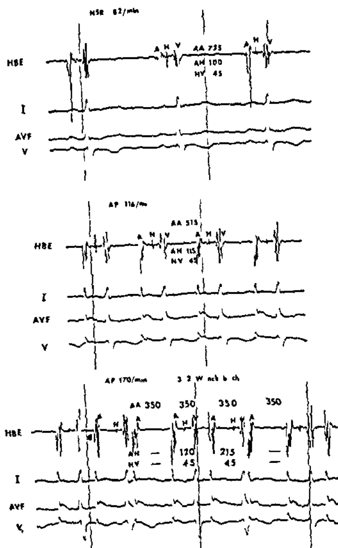


Fig 8 Recordings during NSR in the upper panel atrial pacing at 116 per minute in the middle panel and atrial pacing at 170 per minute resulting in 3 2 Wenckebach are illustrated from patient No 13 a 14 year-old female with no evidence of heart disease The block occurs in the A V node with no change in H V intervals in the three panels

local re entries which were not seen in the surface ECG (Fig 7)

Summary

Bipolar electrode catheter recordings of His bundle electrograms with three simultaneously recorded surface electrocardiographic leads were obtained from 30 pediatric and adolescent patients (aged 3 to 18 years) In 14 patients cardiac murmurs were proved to be innocent by cardiac catheterization The control conduction intervals were compared to those of 13 patients with congenital heart disease and three with acquired heart disease (myocardiopathy rheumatic valvular disease and Friedreich s ataxia)

P R intra atrial (P A) A V nodal (A H) and intraventricular (H V) conduction intervals were measured to the nearest 5 msec Conduction delays were analyzed in each of the three components of the P R interval These delays occurred both in single components of the system as well as in combined conduction delays and were not always demonstrable by surface electrocardiograms The Wenckebach phenomenon induced by atrial pacing was localized to the A V node as well as the His Purkinje system This technique

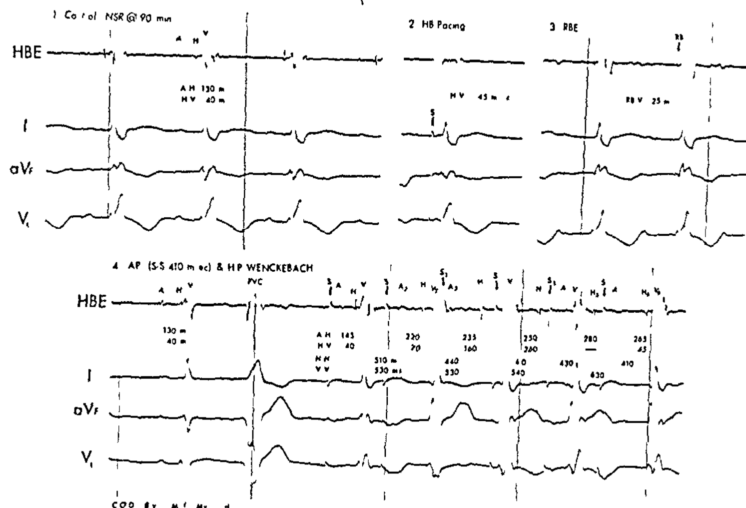


Fig 9 Recordings during NSR in panel 1 His bundle pacing in panel 2 and atrial pacing with His Purkinje (H P) Wenckebach A V block are illustrated from patient No 19 an 8 year old male with myocardiopathy Note the progressive prolongation of H V interval in panel 3 from 40 to 260 msec in the four beats prior to beat No 5 (S5) Beat No 5 is followed by a His deflection (H5) but this is not conducted to the ventricle A_4 is not labeled in the il lustration It falls within the V_3 complex

of intracardiac electrogram recordings is safe does not significantly prolong cardiac catheterization time and often yields unique and useful data concerning A V conduction

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Experimental and laboratory reports

Angiotensin- and norepinephrine-induced myocardial lesions experimental and clinical studies in rabbits and man

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In previous experiments in which the renal effects of high doses of intravenous angiotensin II were studied in the rabbit an unexpected incidental finding was multifocal myocardial necrosis in the majority of the infused animals[1] This raised the possibility that high circulating levels of angiotensin II might in man cause similar lesions and we subsequently described two patients in whom focal myocardial necrosis histologically indistinguishable from that seen in the rabbit was associated with high levels of angiotensin II in peripheral plasma before death[2]

The present paper reports more detailed studies of angiotensin infusion in the rabbit a comparison with the effect of norepinephrine and some additional clinical instances of myocardial lesions possibly induced by angiotensin

Methods

Plasma renin concentration was estimated by the method of Brown and co workers[3] (normal range 4 to 20 *units per liter*) plasma renin substrate by the method of Tree[4] (normal range 0 45 to 1 28 μmol per liter) and plasma angiotensin II in man by the technique of Dusterdieck and McElwee[5] (normal range 5 to 35 pg per milliliter)

The latter method was shown to be applicable to rabbit plasma the only alteration in the technique previously reported for man being that smaller quantities of blood (5 ml) were used Mean recovery of added angiotensin II from rabbit blood was 72 per cent ± 4 4 (S D) range 63 to 75 per cent n = 8 The coefficient of variation of replicate estimations was 9 1 per cent n = 11 A higher normal range was seen in peripheral arterial plasma of the rabbit under the conditions of sampling (see later) than in normal man from 14 to 251 pg of angiotensin II per milliliter of plasma (mean 51 6 ± 40 8 S D n = 71) (see also *Table I*)

Plasma adrenocorticotropin (ACTH) was measured in man by the method of Landon and Greenwood[6] (normal range 12 to 55 pg per milliliter at 0800 to 1000 hours) Plasma 11 hydroxy corticosteroids (11 OHCS) were estimated by the technique of Mattingly[7] the normal upper limit in samples taken between 0800 and 0900 hours being 24 μg per 100 ml Plasma cortisol was estimated by a double isotope dilution derivative

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Table I Changes in plasma angiotensin II and urea concentrations in the various groups of rabbits. Means ±

Group	Procedure	Basal		6 hours		24 hours		48 hours
		Urea (mg %)	AII (pg/mL)	Urea	AII	Urea	AII	Urea
a	Angiotensin II infusion	43±3 2	169±62 2	60*±3 6	11 171±7 583	116†±13 6	12 103±2 976	95 ±17.3
b	Angiotensin II subcutaneous	47±2 1	31±6 2	—	1 047±423 3	183 ±33 0	361±28 6	228‡±15 6
c	Norepinephrine infusion intravenous	49±2 9	74±9 6	39±7 8	285±203 6	33±7 4	208±136 3	39±5 9
d	Saline infusion intravenous	56±8 9	23±2 8	44±5 5	34±6 3	45±8 4	35±10 4	30*±5 0
e	Cephaloridine intramuscular	48±4 0	66±26 8	72 ±3 5	161±99 7	178*±14 0	94±50 0	256†±14 7
f	Bilateral nephrectomy	40±2 7	48±8 5	—	15±2 4	117†	17±1 0	206†±19 9
g	Bilateral nephrectomy plus glycerol	52±5 4	72±48 8	59±15 5	10±1 2	176‡±15 0	28±16 3	259† ± 22 2
h	Sham operation	43±3 0	150±31 0	—	—	48±11 5	166±44 0	51±7 5

Significant diff rences from basal values by paired t test indicated thus * = p < 0 05
† = p < 0 01
‡ = p < 0 001
Proportion of animals with histologic lesions in kidneys and myocardium also given

method (normal range 3 to 20 μg per 100 ml[8] Cortisol secretion rate was estimated as de scribed by James and Caie[9]

New Zealand white rabbits weighing 1 8 to 4 5 kilograms were used for the experimental stud ies all surgical procedures being performed under pentobarbitone anesthesia Intravenous infusions (10 to 15 ml per 24 hours) were made by means of a Harvard pump and polyethylene catheters inserted into a jugular vein as de scribed by Brown Chapuis and Robertson[10] Aseptic precautions were observed throughout blood cultures were taken at the end of the ex periments and were shown to be sterile in all in stances After at least one hour following recov ery from any anesthesia, a 10 ml basal blood sample was taken from the central ear artery for estimation of plasma electrolytes urea and angiotensin II

The following groups of rabbits were then studied further arterial blood samples being taken 6, 24, and 48 hours after starting each ex perimental procedure

Angiotensin infusion Five rabbits were infused with angiotensin II (asp NH_2β amide Ciba) in 0 9 per cent NaCl 0 9 to 1 8 μg per kilogram per minute for 48 hours

Subcutaneous angiotensin Five rabbits re ceived a subcutaneous injection of 3 mg of angiotensin II dissolved in 5 ml of 0 9 per cent NaCl every eight hours for 48 hours

Norepinephrine infusion Five rabbits were in fused for 48 hours with 1 norepinephrine (Win throp) in 0 9 per cent NaCl 0 5 μg per kilogram per minute in four animals and 3 μg per kilo gram per minute in one instance

Saline infusion Five further rabbits were simi larly infused intravenously with saline alone for 48 hours

Intramuscular cephaloridine Five rabbits re ceived a single intramuscular injection of 1 500 mg of cephaloridine (Glaxo) dissolved in distilled water

Further controls Five rabbits had both kidneys removed via separate loin incisions

Five rabbits had both kidneys removed via loin incisions and were then given glycerol 20 ml subcutaneously as described by Brown and co workers[11]

Five rabbits were sham' operated the abdo-

SEM given

All	Kidneys proportion with acute tubular necrosis	Hearts proportion with lesions
7 564±2 760	2 out of 5	All five with extensive confluent necrosis
267±79 1	2 out of 5	All five with extensive confluent necrosis
220±168 9	None out of 5	All five with extensive confluent necrosis
24±4 0	None out of 5	None of five
179 ±29 6	All 5	None of five
25±3 9	None out of 5	One out of five with scattered foci of necrosis none confluent four normal
24±3 1	None out of 5	One out of five with few scattered microfoci of necrosis four normal
258±158 5	None out of 5	None out of five

men and peritoneum being opened and then immediately closed.

Angiotensin was given variously intravenously and subcutaneously to exclude the possibility of abnormalities due to embolism or to chemicals derived from the infusion tubing This aspect was also covered by the experiments in which saline alone was infused. Acute renal failure was induced both by cephaloridine and total nephrectomy so as to eliminate the possibility of the cardiac lesions being related simply to uremia Glycerol was given to one series of nephrectomized rabbits to provide information for comparison with an earlier study [11]

Rabbits in all groups were killed after 48 hours with intravenous pentobarbitone Histologic material from both rabbits and humans was examined by light microscopy following fixation in formalin embedding in paraffin wax and staining of sections by three techniques hematoxylin and eosin Martius Scarlet blue and acid fuchsin Sections from rabbits were coded so that the pathologists (RFM and BG) were unaware of the nature of the experiment performed. After the initial reports had been made the sections were again coded and reviewed Only those abnormalities which were reported on both occasions are included in Table I three instances of dubious lesions being eliminated by this procedure

Results in rabbit experiments

These are summarized in Table I

Significant elevation of blood urea was seen in the animals receiving intravenous or subcutaneous angiotensin intramuscular cephaloridine or subjected to total nephrectomy Blood urea was not increased following norepinephrine administration or sham operation and a slight fall occurred after 48 hours in the animals infused with saline Following bilateral nephrectomy arterial plasma angiotensin II remained low although measurable in all instances this finding is in agreement with the observation by Lever and Robertson[12] of low concentrations of a renin like enzyme in peripheral arterial plasma of the rabbit after removal of both kidneys A similar phenomenon has been observed after bilateral nephrectomy in man [13 16] There was no significant change in mean plasma angiotensin II in the saline infused or sham operated animals Very marked but variable elevation of plasma angiotensin II was seen in the animals given intravenous or subcutaneous angiotensin A slight, but significant increase in mean plasma angiotensin II was also seen in the cephaloridine injected rabbits at 48 hours in agreement with the modest increase in plasma renin concentration we have previously observed in those circumstances [2 17] The four rabbits given the lower dose of norepinephrine (0 5 μg per kilogram per minute) did not show systematic changes in plasma angiotensin II However the animal receiving the high dose (3 μg per kilogram per minute) had increased plasma angiotensin II levels throughout the infusion (76 pg per milliliter basal 1 091 611 and 891 pg per milliliter at 6 24 and 48 hours respectively)

Renal histology No abnormalities were seen in the kidneys of rabbits infused with norepinephrine or saline alone or those animals which were sham operated The kidneys removed at bilateral nephrectomy were similarly normal By contrast and as in previous studies [1] the kidneys of four of the ten animals given angiotensin showed ischemic necrosis of proximal, distal and collecting tubules evidence of protein leakage in

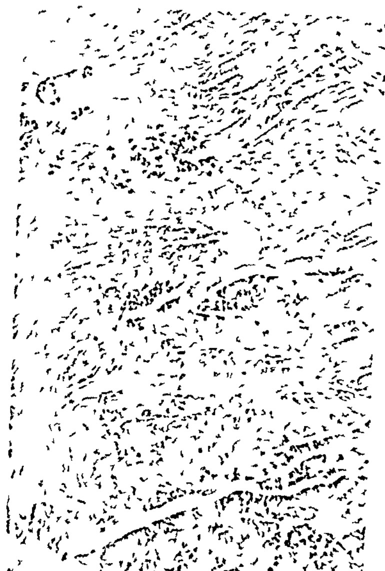


Fig 1 Low power micrograph of myocardium of rabbit infused with angiotensin Four clearly separate foci of muscle necrosis (darker zones) are present Hematoxylin and eosin ×150



Fig 2 Myocardium of rabbit infused with angiotensin. The dead muscle cells (grey to black) appear in the lower half of the micrograph Hematoxylin and eosin × 350

glomeruli and hyaline casts No arterial or arteriolar lesions were seen All five animals receiving cephaloridine showed extensive necrosis localized to the proximal tubules as reported in other studies [17 21]

Cardiac histology Extensive frequently confluent, multifocal microscopic myocardial necroses were seen in all of the ten rabbits given angiotensin (Figs 1 and 2) The low power photomicrograph (Fig 1) illustrates the multifocal nature of the myocardial lesions in an angiotensin infused rabbit Fig 2 shows adjacent normal and necrotic myocardium at a higher magnification Often, marked histopathologic variations were observed between different lesions in the same block presumably, in part the result of varying duration from onset to death Many examples were seen of single blocks of tissue exhibiting all gradations from degenerative muscle cell changes including poorly staining muscle striations in otherwise intact cells tigroid banding of cytoplasmic constituents with intact cell nuclei and densification of nuclei, up to definite necrosis In the oldest lesions there was disappearance of the dead cells and early replacement by granulation tissue Microangiopathy was not observed in the hearts

All five rabbits infused with norepinephrine had myocardial lesions which were histologically indistinguishable from those in the animals given angiotensin

By contrast, myocardial histology was entirely normal in all the saline infused, cephaloridine treated and sham operated animals. Eight of the ten rabbits subjected to bilateral nephrectomy also had normal cardiac histology but two



Fig 3 Micrograph of human myocardium of Case 1 The dead muscle cells (black) appear in the lower half of the picture Hematoxylin and eosin, ×300

animals showed a few scattered nonconfluent foci of necrosis Minor myocardial changes of this nature have been found by us in a similar proportion of laboratory rabbits killed without being subjected to experimental procedures These spontaneous lesions may well be the result of infection with *Toxoplasma gondii* which has been shown to cause similar myocardial abnormalities in mice[22] and rats[23] However in the dog bilateral nephrectomy can cause myocardial hemorrhages necrosis and fibrosis[79-81] and it is possible that similar effects might be produced in the rabbit.

Clinical observations

Cases 1 through 3 have been reported briefly earlier[2,11]

Case 1 A 26 year old multiparous woman presented with malignant hypertension and urographic evidence of chronic pyelonephritis giving a history of repeated urinary infections mainly in pregnancy Renal function was moderately impaired (creatinine clearance 26 ml per minute) and plasma renin concentration was slightly elevated at 31 units per liter Blood pressure was initially well controlled with methyldopa alone and in the following three months both plasma renin (10 to 25 units per liter) and angiotensin II (23 to 27 pg per milliliter) levels in peripheral blood were normal or only slightly elevated Over the next year renal function deteriorated progressively and blood pressure became increasingly difficult to control with a variety of hypotensive drugs Because of the renal impairment hemodialysis became necessary peripheral plasma angiotensin II two hours before the initial dialysis being distinctly high (138 pg per milliliter) Coil pressure and bath fluid composition were adjusted so as to remove water and sodium from the patient. During dialysis blood pressure fluctuated widely from 230/150 to 80/50 mm Hg Four hours after the start of the procedure the patient became disoriented and the diastolic pressure rose to 160 mm Hg Diazoxide 300 mg was given intravenously but within a few minutes cardiac and respiratory arrest occurred The heart restarted following external cardiac massage and an intravenous bolus of 2 μg of epinephrine hydrochloride However the patient died without regaining consciousness 24 hours later two further plasma angiotensin II measurements being 63 and 29 pg per milliliter respectively 5 and 20 hours after cardiac arrest

Postmortem examination confirmed the presence of shrunken scarred probably pyelonephritic kidneys The main coronary arteries were atheromatous but free from thrombosis Recent multifocal myocardial infarction was found in two out of three randomly selected blocks from the left ventricle up to 12 micro infarctions being found in each section of 2 by 3 cm (Fig 3) The largest infarction seen was 3 mm in diameter No histologic abnormalities were noted in numerous sections examined of the cerebrum and cerebellum The brain stem however showed several small hemorrhages focal neuronal necrosis and mild patchy polymorphonuclear infiltration suggesting terminal infarction

Case 2 A 52 year old woman was admitted with malignant hypertension left ventricular

failure, and renal impairment (blood urea levels 152 and 202 mg per 100 ml, respectively on the first two days of admission) Because of the severity of the hypertension (220/170 mm Hg) intravenous diazoxide was given This controlled the arterial pressure, but blood urea rose progressively to 408 mg per 100 ml by the fifth day Plasma angiotensin II levels also increased (values 53 77, 71, and 152 pg per milliliter during the first week following admission) Peritoneal dialysis was begun but the patient died early in the morning of the eleventh day following admission plasma renin concentration (238 units per liter) and plasma angiotensin II (323 pg per milliliter) both having been markedly elevated 15 hours earlier

Postmortem examination showed widespread fresh microscopic infarctions similar to those of Case 1 together with a larger fresh infarction involving the interventricular septum The coronary arteries were free from atheroma Also found were a 2 mm diameter hematoma in the left cerebellar hemisphere a 6 mm diameter infarction in the pons and fibrinoid necroses in cerebral arterioles

Case 3 A 37 year old man presented with malignant phase hypertension, renal biopsy showing changes suggestive of chronic pyelonephritis Blood pressure was difficult to control with large doses of a variety of hypotensive and diuretic drugs and six months later blood urea had risen to 72 mg per 100 ml Plasma concentrations of renin and angiotensin II were elevated (32 units per liter and 194 pg per milliliter) Six weeks later, further deterioration of renal function (creatinine clearance 1 ml per minute, serum creatinine 12 4 mg per 100 ml, serum urea, 200 mg per 100 ml) necessitated the introduction of regular hemodialysis Plasma concentrations of renin, renin substrate and angiotensin II were by now grossly raised (ranges 64 to 114 units per liter, 5 0 to 6 0 µmol per liter and 1,900 to 5 049 pg per milliliter) The disproportionate elevation of angiotensin II relative to renin was thought probably to be due to the increased concentration of renin substrate

Hypertension was uncontrolled even with the introduction of dialysis but on two occasions during the next three weeks once within an hour following hemodialysis cardiac arrest occurred A transvenous pacemaker was therefore, inserted The electrocardiograph at this stage showed features of left ventricular hypertrophy but not of ischemia Serum transaminase levels remained within the normal range

Because of the intractable hypertension associated with grossly elevated renin and angiotensin II levels bilateral nephrectomy was performed three weeks after the start of hemodialysis Plasma renin and angiotensin II concentrations fell to subnormal levels within 48 hours Two further episodes of cardiac arrest occurred five and six days after nephrectomy and the electrocardiograph developed elevated ST segments in Leads V_1 and V_2 with T wave inversion in Leads 1 through 3 and V_4 through V_6 suggestive of widespread ischemia Serum transaminases again remained in the normal range, although lactic dehydrogenase showed persistent slight elevation (216 to 245 mU per milliliter, normal < 195) Throughout the period of recurrent attacks of asystole serum calcium remained within the range of 7 7 to 9 8 mg per 100 ml serum potassium 3 2 to 5 6 mEq per liter and serum bicarbonate 17 to 26 mMol per liter Subsequently the cardiac status stabilized and the pacemaker was removed

Following total nephrectomy blood pressure was readily controlled by regular hemodialysis alone and the patient has remained well with no subsequent attacks of asystole in the ensuing 3½ years

Case 4 A 30 year old man was admitted with clinically obvious Cushing's syndrome severe hypertension (210/150 mm Hg) and bilateral retinal hemorrhages and exudates Plasma 11 OHCS were increased with abolition of the normal circadian rhythm (28 and 30 µg per 100 ml at 0900 hours 31 and 38 at 2100 hours) Cortisol secretion rate was markedly increased (102 µg per 24 hours) Plasma ACTH levels were high both at 0900 hours (60 and 65 pg per milliliter), and at 2100 hours (80 90 and 70 pg per milliliter) and were not suppressed in the normal way by dexamethasone 8 mg daily for two days (30 pg per milliliter at 0900 85 pg per milliliter at 2100 hours) Creatinine clearance was impaired (36 ml per minute) while serum creatinine (2 1 mg per 100 ml) and urea (75 mg per 100 ml) were elevated Plasma renin (6 to 11 units per liter) and angiotensin II (17 to 25 pg per milliliter) concentrations were within the normal range

Bilateral adrenalectomy was performed renal biopsy taken at the operation showing vascular

lesions of malignant hypertension Following adrenalectomy plasma cortisol (2 9 to 4 4 μg per 100 ml) and 11 OHCS (10 to 13 μg per 100 ml) fell to low levels and there was no response to ad ministered ACTH (post ACTH plasma cortisol 3 2 and 11 OHCS 12 0 μg per 100 ml respectively) Blood pressure however remained elevated and in addition to corticosteroid replacement ther apy hypotensive drugs (methyldopa and pro pranolol) were started The retinal lesions gradually healed Creatinine clearance de creased progressively to 3 ml per minute and serum creatinine and urea rose to 9 5 and 250 mg per 100 ml respectively one year after adrenalectomy Blood pressure again became dif ficult to control and retinal hemorrhages and ex udates reappeared. At this stage plasma renin (47 to 84 units per liter) and angiotensin II (97 to 328 pg per milliliter) concentrations were markedly elevated. Retrosternal pain occurred strongly suggestive of myocardial infarction and inversion of T waves appeared in the lateral leads of the electrocardiograph but there was no evidence of transmural infarction Serum trans aminases remained persistently within the nor mal range although as in Case 3 serum lactic dehydrogenase was elevated throughout a period of four weeks (249 to 328 mU per milliliter nor mal < 195) This increase was shown to be due to elevation of the isoenzymes LD_1 and LD_2 which are found mainly in cardiac muscle erythro cytes and kidney and in LD_5 which occurs chiefly in skeletal muscle and liver

Diazoxide initially given intravenously and subsequently by mouth (800 to 1 200 mg daily) effectively controlled the blood pressure but creatinine clearance fell further to 2 ml per minute and fluid retention unresponsive to di uretics developed Regular hemodialysis was therefore begun Blood pressure was eventually controlled with a combination of regular hemo dialysis and oral diazoxide 700 mg daily but renin (100 to 130 units per liter) and angiotensin II (200 to 920 pg per milliliter) concentrations in peripheral plasma rose further Bilateral nephrectomy was performed three months *after* the episode of chest pain both renin and angiotensin II falling to subnormal values The kidneys were grossly shrunken (each approxi mately 90 grams) and on histologic examination showed extreme hypertensive nephrosclerosis. Following total nephrectomy hypotensive drugs were withdrawn and blood pressure control was maintained by regular hemodialysis alone A ca daver kidney was implanted four months later blood pressure control remaining excellent sub sequently No further cardiac episodes have oc curred in the subsequent two years

Case 5 A 21 year old woman with hyperten sion of three years known duration was admit ted to another hospital with a blood pressure of 235/140 mm Hg and bilateral papilledema hem orrhages and exudates Right sided renal artery stenosis was suggested by excretion urography which showed earlier appearance of dye in creased contrast density and diminished filling of pelvis and calyces on the right and this was confirmed on renal arteriography Operation was considered inadvisable at that time and anti hypertensive drugs were started Control was dif ficult to achieve however and *two years later* she was referred to this unit with an arterial pressure around 240/150 mm Hg and recurrence of bilateral retinal hemorrhages and exudates Ureteric catheterization studies confirmed se *vere right renal artery* stenosis Plasma angio tensin II was 106 pg per milliliter in the periph eral artery 141 pg per milliliter in the right renal vein and 54 pg per milliliter in the left *renal vein* the corresponding renin concentra tions being 29 42 and 24 units per liter It was decided to operate on the renal artery clonidine *therapy* (1 5 mg three times daily) being con tinued until four days before surgery and then stopped.

At operation a Dacron graft was inserted be tween the aorta and distal right renal artery The pressure gradient across the stenosis at the start of the operation was 96/60 12/6 millimeters *Hg* and after reconstruction 150/106 118/96 millimeters Hg The patient s condition remained satisfactory for 30 hours after operation al though the diastolic pressure remained between 120 and 150 millimeters Hg Then there was an *abrupt fall* of pressure to unrecordable levels and the patient became unconscious Electrocardio graphy showed no specific abnormalities *In* travenous infusion of 1 norepinephrine 2 milligrams over four hours (approximately 0 16 microgram per kilogram per minute) raised the arterial pressure to between 100/70 and 120/80 millimeters *Hg and* the subsequent administra tion of intravenous metaraminol tartrate 90 milligrams over twelve hours sustained these

levels However, the patient then died without regaining consciousness

At postmortem examination, the arterial graft was found to be patent. The right kidney was essentially normal histologically whereas the left kidney showed extensive changes of hypertensive nephrosclerosis these findings were consistent with the concept of the renal artery narrowing protecting the right kidney from the adverse effects of the severe hypertension The affected renal artery showed fibromuscular hyperplasia A left middle cerebral artery thrombosis was present associated with cerebral infarction There was atheroma of the main coronary arteries without thrombosis Widespread multifocal areas of myocardial necrosis up to 5 mm in diameter were present, many being in regions supplied by nonatheromatous coronary vessels Necrosis was confirmed by demonstrating absence of succinic dehydrogenase

Discussion

The present studies have confirmed and considerably extended our previous observations on angiotensin induced myocardial necrosis and acute renal failure [1 2] Angiotensin II given either intravenously or subcutaneously consistently induced extensive multifocal confluent microscopic myocardial necrosis Histologically indistinguishable lesions were induced in other rabbits by the infusion of norepinephrine Very similar myocardial abnormalities were found postmortem in three patients known to have had high plasma levels of angiotensin II shortly before death One of these had however also been infused with norepinephrine and metaraminol and another had received a single intravenous injection of epinephrine Moreover one patient had sustained a thrombosis of a middle cerebral artery, another patient had a cerebellar hematoma and a pontine infarction and the third patient showed multiple microscopic infarctions in the brain stem

It has long been known that myocardial lesions can result from the administration of epinephrine,[24 28 70] norepinephrine [29 31] isoproterenol,[32 34] or metaraminol,[77 78] and apparently identical abnormalities have been described in the heart muscle of patients with pheochromocytoma [35 38]

Similar lesions can also be induced in the myocardium by intracranial hemorrhage [39 42 71] The severity of this necrosis can be mitigated by pretreatment with reserpine suggesting that catecholamines are involved in pathogenesis here also [43]

Sevitt[72] has noted the frequent occurrence of subendocardial hemorrhages following death from severe trauma, burns head injury or intracranial lesions

Despite a spectrum of histologic abnormalities in these various situations similar to those seen in the present studies, many authors have persistently avoided the use of the word 'necrosis and have substituted 'myocarditis" The latter term has been used in a sense similar to that pertaining to diphtheritic myocarditis This in its fully developed form, comprises multifocal myocardial cell necrosis while its minor expressions include less severe and possibly reversible myocardial alterations with interstitial inflammation

Numerous investigations have shown that the administration of angiotensin to experimental animals stimulates cathecholamine release [44-49] Westfall and Peach[50] reported an increase in norepinephrine levels in rabbit heart after angiotensin was given while Farr and Grupp[51] suggested that angiotensin at low doses caused its cardiac effects[52] mainly by stimulation of the ganglion cells of the cardiac sympathetic nerves.

It remains uncertain whether the myocardial abnormalities seen in the present studies are directly due to increases in circulating angiotensin II or are mediated via catecholamines This aspect requires further study In the dog it has been shown that the continuous infusion of angiotensin into the coronary artery causes sustained constriction of the large arteries, while the smaller resistance vessels rapidly escape from the vasoconstrictor effects [73]

Scornik and Paladini[74 75] showed that the intravenous infusion of norepinephrine in the dog caused an increase in angiotensin blood level In the present studies, an increase in plasma angiotensin II was seen only at the higher dose of norepinephrine Since cardiac lesions were observed at both dose rates of norepinephrine such lesions appear not to have been mediated via a rise in plasma angiotensin II

As in the earlier experiments [1] administration of angiotensin II at high dosage to rabbits also consistently induced acute renal failure frequently associated with tubular necrosis Norepinephrine by contrast did not in the doses employed here cause renal abnormalities Thus

despite the similarity of the cardiac effects of angiotensin and norepinephrine the renal effects of the two drugs were very different Angiotensin was in the present studies, given in very high doses the critical angiotensin II plasma level required to produce myocardial necrosis remains to be determined The much lower although significantly raised plasma angiotensin II concentrations occurring late after cephaloridine administration were either insufficiently high or had risen too recently to have caused visible myocardial damage The absence of myocardial necroses in the animals receiving cephaloridine shows that these lesions are unlikely to be a feature of acute renal failure per se since this was more severe in the cephaloridine series than in either group given angiotensin As mentioned, bilateral nephrectomy might have different myocardial effects from cephaloridine

Huttner Rona and More[53] noted fibrin deposition within cardiac muscle cells in experimental renal hypertension in the rat In their experiments such myocardial abnormalities were associated with fibrinoid vascular lesions Although cardiac microangiopathy was not observed in the present series it is possible that intramyocardial fibrin deposition was a contributory factor in the genesis of the necrosis Myocardial necroses infarcts hemorrhages and fibrosis generally associated with overt vascular lesions have been described in renal and malignant hypertension in several species[62 65] Similar abnormalities have also been induced by the administration of renal extracts in various experimental circumstances and have been noted after the injection of angiotensin to uninephrectomised rats pretreated with desoxycorticosterone and salt.[66] The present findings could well be relevant to some aspects of the earlier studies

The five patients described may have had similarly induced cardiac lesions to those seen in the rabbits although the evidence is circumstantial and this, therefore remains at present speculation Cases 1 2 and 5 all suffered fatal heart attacks having been known to have high peripheral plasma concentrations of renin and angiotensin II shortly before Histologically identical lesions were found in all three cases. A marked rise in angiotensin II might well have been provoked in Case 1 by the hemodialysis during which cardiac arrest occurred, and a similar increase could have been induced in Case 5 by renal artery surgery

Postmortem examinations on Cases 1 and 5 both young women revealed coronary atheroma in the absence of thrombosis Impaired coronary artery perfusion could possibly predispose to focal microscopic lesions although in both patients these were found in areas supplied by non atheromatous coronary vessels

It should be emphasized that in all three cases examined postmortem there were alternative explanations for the myocardial necroses All of the cases had intracranial vascular lesions and two of the subjects had received therapeutic catecholamines A further possibility in Case 5 is that following the withdrawal of clonidine before operation there may have been a sudden rise in circulating catecholamines[76] although this was not clinically apparent

Alternative connections worth considering are that the myocardial necroses observed in patients with intracranial lesions or after severe trauma[39 42 71 72] might be mediated via angiotensin II which could well be increased acutely in such circumstances

Cases 3 and 4 survived, and myocardial histology is therefore not studied. As in Cases 1, 2 and 5 neither showed clear electrocardiographic or serum enzymic evidence of myocardial infarction but this would not be unexpected if widespread but microscopic lesions only were present Both patients were found repeatedly to have very high peripheral plasma levels of angiotensin II and in both cases the cardiac attacks ceased after bilateral nephrectomy

If the myocardial necroses observed here in man are attributable to angiotensin there are obvious clinical implications. Angiotensin which was suggested as a possible therapeutic agent in states of hypotension with peripheral circulatory failure[54 55] is now seen to have potentially serious adverse renal and cardiac effects[1 2] Sudden death has been reported during angiotensin infusion[56 57] but myocardial lesions were not noted in either instance Similar plasma angiotensin II concentrations to those reported here have been seen by us in patients with untreated Addison s disease (up to 295 pg per milliliter) in severe dehydration (up to 584 pg per milliliter)[18] and in children with Desmit s syndrome[58] (up to 2 168 pg per milliliter) without clinical evidence of cardiac problems. Possibly a consistent high level

of angiotensin II is better tolerated than a sudden rise, if this is so, sodium depleting hemodialyses the administration of natriuretic drugs and renal artery surgery might be particularly hazardous in susceptible patients Blood pressure elevation could be a necessary factor[85] for the production of the myocardial necroses

Brunner and co workers[59] suggested that hypertensive patients with high plasma renin activity (and by implication elevated plasma angiotensin II) might be particularly susceptible to heart attacks and strokes whereas those with low renin levels might be relatively protected Although this hypothesis could be relevant to the present studies, Brunner[60] has suggested that the patient most at risk seems likely to have a relatively fixed high plasma renin level Furthermore it is uncertain whether the cardiac lesions in the patients of Brunner and co workers[59] are histologically similar to those reported here It should also be emphasized that the epidemiologic validity of the paper of Brunner and co workers[59] has been seriously challenged[61 64] and subsequent workers have been unable to confirm the original findings[65 68] Despite defense of their hypothesis by Brunner Sealey, and Laragh[69] it appears to us that their original retrospective survey[59] involved too many uncontrolled or unassessed variables to permit evaluation of the role of renin in prognosis

It is emphasized that the clinical aspects of the present paper are also very speculative there being alternative explanations for the myocardial necrosis in all three patients coming to necropsy However determination of the critical plasma angiotensin II concentration range for the production of cardiac lesions should permit firmer conclusions on these aspects in the future

Summary

The ability of large doses of exogenous angiotensin II to cause widespread multifocal microscopic myocardial necrosis in the rabbit has been confirmed

Angiotensin II also consistently produced acute renal failure with less consistently renal tubular necrosis

Norepinephrine infusions caused histologically indistinguishable myocardial lesions, but did not detectably affect renal function or histology

Severe renal failure induced by bilateral nephrectomy (with or without concurrent glycerol administration) was not associated with similar cardiac lesions

Acute renal failure of comparable or greater severity to that induced by angiotensin II was produced by intramuscular cephaloridine, and was not associated with cardiac lesions

Rabbits infused with saline intravenously or "sham' operated by simply opening and closing the peritoneal cavity did not develop renal failure and showed no cardiac or renal lesions histologically

Myocardial lesions apparently identical to those seen in the rabbits were observed post mortem in three patients known to have had high circulating levels of angiotensin II before death, although in all three cases alternative explanations are possible

Unexplained arrhythmia cardiac arrest and central chest pain without clear cardiographic or serum enzyme evidence of myocardial infarction occurred in two other subjects with very high plasma levels of angiotensin II These attacks ceased after bilateral nephrectomy and a consequent fall in plasma angiotensin II

The cardiac attacks in these five patients all occurred during or shortly after procedures, such as sodium depleting dialysis renal artery surgery or diazoxide administration, known to cause increases in plasma concentrations of renin and angiotensin II

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Altered myocardial oxygen consumption after coronary occlusion in anesthetized dogs

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Contractility tension and heart rate are major determinants of myocardial oxygen consumption ($M\dot{V}O_2$†)[1-4] The extent of tissue damage following myocardial infarction appears to be related to the ratio between oxygen supply and demand in ischemic tissue Furthermore factors which alter this ratio also alter the extent of experimental myocardial infarction[10] However little information is available concerning the changes in left ventricular oxygen consumption after acute myocardial infarction[9] Moreover elucidation of the effect of infarction per se on MVO_2 would facilitate the laboratory and clinical use of this parameter in the investigation of myocardial infarction Accordingly the present study was designed to examine the effect of acute coronary occlusion on myocardial oxygen consumption in dogs and to characterize the alterations of MVO_2 induced by perturbation of heart rate and the blood pressure in animals with experimental myocardial infarction

Methods

Experimental preparations Studies were performed with nine mongrel dogs weighing 20 5 to 35 0 kilograms anesthetized with pentobarbital sodium (30 mg per kilogram) Ventilation was maintained with a positive pressure respirator and 100 per cent O_2 The chest was opened by bilateral thoracotomy and the animals were placed on right heart bypass as described in detail previously[15] In brief the venae cavae and the right ventricle were cannulated and blood from the systemic veins and the coronary sinus was drained separately into a reservoir by gravity The systemic venous and coronary sinus blood was passed through a heat exchanger and pumped into the pulmonary artery at a constant flow rate (1 4 L per minute to 3 4 L per minute) A cannula was inserted into the abdominal aorta and connected to a reservoir of blood to control systemic blood pressure Heart rate was controlled (130 to 200 beats per minute) by right atrial stimulation after the sinus node had been crushed. The left anterior descending coronary artery was dissected free approximately 2 cm distal to the bifurcation of the left coronary artery and distal to at least one and usually two major branches The left anterior descending coronary artery (LAD) was occluded with a Schwartz arterial clamp Epicardial ST segment maps were obtained from eight to 10 sites by a method previously described,[10] and the sum of all ST segment elevations (ΣST) was used to assess the severity of ischemia Single plane left ventricular cineangiograms (lateral projection) were obtained after injection of 1 milliliter per kilogram of 75 per cent hypaque through the left ventricular pressure cannula and were recorded at 200 f p s with a Philips Medio 50 cineangiographic unit.

Measurements Coronary blood flow was meas

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†Unless qualified, $M\dot{V}O_2$ is used to represent oxygen consumption of the whole heart.

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Infarction				
dP/dt/ DP AT 40	CBF (ml/ min.)	A VO_2 diff	MVO_2 (ml/ min.)	ΣST
18 4	200	7 05	14 10	14
14 6	118	14 60	17 22	15
18 7	66	18 10	11 94	36
18	54	14 32	7 73	22
9	124	9 95	12.33	54
13 2	64	16 69	10 68	34
11 1	90	15 49	13 94	22
12 5	86	14 66	12 60	48
14 6	76	16 70	12 69	21
14 45	97 55	14 17	12.58	29 5
±1 13	±15 03	±1 17	±0 86	±4 7
NS	<0 01	<0 05	<0 001	<0 002

ments The mean was 15 02 ± 1 12 ml. per 100 ml of blood in the control state compared to 14 17 ± 1 13 ml per 100 ml of blood after coronary artery occlusion ($p < 0.05$) Coronary blood flow fell in each case by 3 per cent to 11 per cent of the control flow with a mean reduction of 5 6 per cent ($p < 0.01$) The left ventricular end diastolic pressure (LVEDP) rose significantly in each case from 2 27 ± 0 33 to 4 77 ± 0 49 mm Hg after coronary artery occlusion Left ventricular end diastolic volume increased in five out of the six experiments (from 31 1 ± 4 1 to 35 6 ± 5 4 ml) No consistent change was observed in left ventricular dP/dt determined at a developed pressure at 40 mm Hg (Table I)

To assess the extent of ischemic injury epicardial ST segment maps (ΣST) were obtained immediately prior to and 15 minutes after coronary artery occlusion As shown in Table I the largest increase in ΣST was in the two animals with the greatest ΔMVO_2 (experiments 5 and 8) ΔMVO_2 correlated well with the ΣST ($r = 0.72$ $p < 0.05$)

Effect of changes in heart rate on MVO_2 after coronary artery occlusion Heart rate was increased in six dogs by atrial pacing before and after coronary artery occlusion while systolic pressure and cardiac output were held constant. Fig 2 A depicts the results of these experiments Increasing heart rate prior to coronary artery occlusion resulted in an increase in MVO_2 ($\Delta MVO_2 = 0.75 \pm 0.1$ ml. per minute per 10 beats per minute After coronary artery occlusion when heart rate was changed comparably MVO_2 increased by 0 42 ± 0 7 ml per minute per 10 beats per minute However, the increase after coronary occlusion was significantly less than that observed prior to coronary artery occlusion ($p < 0.01$)

Effects of alterations of systolic pressure on MVO_2 after coronary artery occlusion While heart rate and cardiac output were held constant MVO_2 was determined prior to and after coronary artery occlusion at selected systolic arterial blood pressures The results are shown in Fig 2 B When systolic pressure was increased, MVO_2 increased both prior to (0 57 ± 0 11 ml per minute) and after coronary artery occlusion (0 47 ± 0 04 ml per minute) The increase in MVO after coronary artery occlusion was significantly less than that seen prior to occlusion with the same increment in systolic pressure ($p < 0.05$) The mean change in MVO per 5 mm Hg systolic pressure changes was 18 per cent less than that prior to occlusion

Discussion

Results from the present study demonstrate that under controlled conditions oxygen consumption of the whole heart (MVO_2) falls after acute coronary occlusion and that the magnitude of the fall in MVO_2 is related to the severity of ischemia assessed by epicardial ST segment elevation Both coronary blood flow and the A VO_2 difference decreased after coronary occlusion When heart rate or systolic blood pressure were varied after coronary artery occlusion the changes in MVO_2 were directionally similar to those observed prior to coronary occlusion but of much smaller magnitude

The fall in MVO_2 after infarction may be due simply to loss of functional myocardium. This interpretation is supported by the correlation between the extent of ST segment elevation and the fall in MVO_2. If there were no change in the flow per unit volume of functional myocardial tissue coronary blood flow would diminish after coronary artery occlusion In fact, coronary flow decreased in all experiments after coronary artery occlusion However the fall in coronary flow did not account entirely for the decrease in MVO_2 observed Overall reduction of MVO_2 resulted from a combination of decreased flow and decreased coronary A VO_2 difference Coronary

Table I Summary of hemodynamic and MVO_2 data before and after coronary artery occlusion

	Control										
Exp	*Heart rate*	*Peak LVP*	*LVEDP*	*dP/dt/ DP AT 40*	*CBF (mL/ min.)*	*A VO_2 diff*	*MVO_2 (mL/ min.)*	*ΣST*	*Heart rate*	*Peak LVP*	*LVEDP*
1	171	105	4 0	18 4	206	7 78	16 02	0	171	110	5 0
2	160	125	2 5	14 6	126	14 85	18 71	0	148	130	7 0
3	150	110	1 5	22 2	74	16 77	12 40	10	141	105	3 0
4	139	85	1 0	18	56	15 88	8 89	4	140	85	2 0
5	154	155	1 0	11 1	126	11 39	14 35	2	154	155	4 0
6	117	105	3 0	12 5	72	17 67	12 48	8	121	102	5 5
7	171	100	3 0	12 5	95	15 87	15 07	0	171	105	6
8	190	115	2 0	14 6	94	16 84	15 82	8	190	112	7
9	130	115	3 5	17 5	82	18 18	14 60	5	130	112	5
Mean	153 5	113 8	2 27	15 7	103	15 02	14 26	4 1	151 7	112 88	4 77
±S E M	±7 54	±6 27	±0 33	±1 19	±15 02	±1 12	±0 92	+1 29	±7 3	±6 55	±0 49
									P NS	NS	<0 001

Summary of hemodynamic and MVO_2 data before and after coronary artery occlusion LVP left ventricular pressure LVEDP left ventricular end diastolic pressure CBF coronary blood flow dP/dt/DP at 40 = dP/dt at developed pressure of 40 mm Hg NS not significant.

ured by timed collection of right ventricular drainage In this preparation right ventricular drainage represents 95 per cent of left ventricular flow minus the left ventricular Thebesian flow [5] Simultaneous systemic arterial and coronary venous blood samples were analyzed for O_2 content by the method of Van Slyke and Neil [13] $M\dot{V}O_2$ was calculated from the product of coronary blood flow and coronary AVO_2 difference

Aortic and left ventricular pressures were monitored with wide bore steel cannulae directly attached to Statham P23Db transducers The cannula transducer systems had a flat amplitude response to a frequency of 40 Hz The first derivative of a left ventricular pressure (dP/dt) was measured with an electronic differentiator This system had a 90 degree phase shift for 0 to 160 Hz All recordings were made on Brush Mark 200 rectilinear ink recorders Left ventricular end diastolic volumes were calculated using the area length method for an ellipse as described by Sandler and Dodge [12]

Experimental Protocol Experiments were designed to examine the effect of coronary artery occlusion on MVO_2 when heart rate mean aortic pressure, and cardiac output were held constant and to investigate the effects of imposed changes in heart rate and arterial pressure on MVO_2 before and after coronary artery occlusion

In nine experiments, MVO_2 epicardial ST segment maps and left ventricular cineangiograms were obtained after placing the animals on right heart bypass While heart rate, blood pressure and cardiac output were maintained constant, the LAD coronary artery was occluded and 20 minutes later measurements of MVO_2 were repeated The effects of increasing heart rate before and after coronary artery occlusion were examined in six of these dogs In these six experiments heart rate was increased an average of 50 beats per minute (from 130 to 180) and arterial pressure and cardiac output were maintained constant. $M\dot{V}O_2$ was measured again 60 to 90 minutes after coronary artery occlusion before and after a similar (50 beats per minute) change in heart rate Similarly MVO_2 was measured before and after arterial pressure was increased by an average of 29 mm Hg from 98 mm Hg to 127 mm Hg prior to and 60 to 90 minutes after coronary artery occlusion

Results

Effect of coronary artery occlusion on MVO_2 In all nine experiments MVO_2 decreased following coronary artery occlusion (Fig 1) After coronary artery occlusion *MVO_2 fell from a mean of* 14 26 ml. per minute (± 0 92 S E M) to 12 58 ml per minute (± 0 86) ($p < 0\ 001$) The fall in MVO_2 resulted from significant reduction of both coronary A VO_2 difference (ΔAVO_2) and coronary blood flow ΔAVO_2 fell in eight out of nine experi

change in volume compared to that seen with a normally compliant ventricle Accordingly developed tension would be less and the increase in MVO_2 associated with the increase in afterload would be smaller

The present studies were performed relatively early during the course of coronary occlusion and may not correspond to observations in patients later following myocardial infarction Moreover in man the pathology of coronary artery disease is more complex and this may limit the application of these results to the clinical setting Nevertheless on the basis of results in this study determinations of MVO_2 in patients to assess the efficacy of therapeutic interventions should be interpreted with caution Changes in MVO_2 may not be comparable in different patients if they are dependent upon the extent of tissue damage Perhaps more importantly reduction of MVO_2 may not reflect favorable reductions of oxygen requirements but rather extension of infarction

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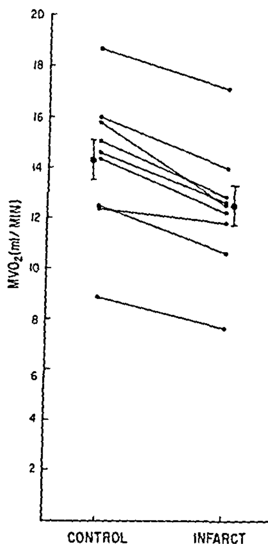


Fig 1 Myocardial oxygen consumption ($M\dot{V}O_2$) before and after coronary occlusion Bars show mean ± S E M MVO_2 fell significantly in all experiments

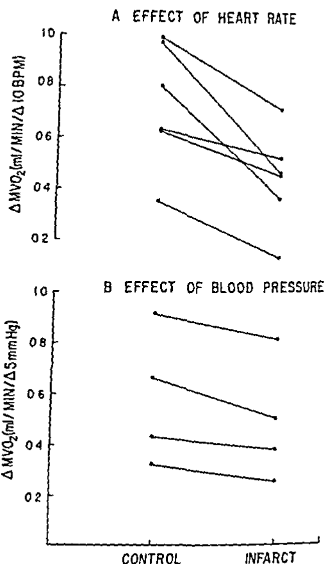


Fig 2 Panel A Effect of increased heart rate on myocardial oxygen consumption (Δ MVO_2 per 10 beats per minute increase in heart rate) before and after coronary artery occlusion. ΔMVO_2 was significantly less after coronary artery occlusion ($p < 0.01$) Panel B Effect of increased systolic pressure on $M\dot{V}O_2$ before and after coronary occlusion. ΔMVO_2 was significantly less after coronary occlusion ($p < 0.05$)

flow in unoccluded vessels has been shown to increase after experimental coronary artery occlusion [8,11,14] Thus the decreased A VO_2 difference observed in the present study may have resulted from increased coronary flow and oxygen content in nonoccluded vessels [14]

When heart rate was increased after coronary artery occlusion MVO_2 increased. However, the absolute and per cent changes in MVO_2 were much smaller than those prior to occlusion This could be due to a net loss of functional myocardium after coronary occlusion Acceleration of heart rate after coronary artery occlusion increases the extent of myocardial damage [10]

The smaller ΔMVO_2 associated with acceleration of heart rate after infarction may be influenced by progression of ischemic injury and loss of functional myocardium due to extension of infarction consequent to tachycardia This interpretation is supported by the observed increase in ΣST

Increases of arterial pressure resulted in a smaller increase in MVO_2 after occlusion compared to that seen prior to coronary artery occlusion with comparable changes in peak left ventricular pressure The explanation for this is not clear The smaller increase observed after coronary artery occlusion again could be related to the loss of functional myocardium Another possibility is that increased afterload after coronary artery occlusion may not alter ventricular volume to the same extent as it does in the normal heart because of altered compliance of the ventricle [2,3,6,7] If the ventricle is less distensible after acute coronary artery occlusion [2,6] increased afterload would result in a more modest

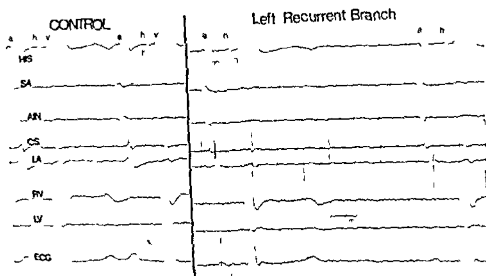


Fig 1 Direct and reflex effects of stimulation of a branch of the left recurrent cardiac nerve Both vagi are intact. His His bundle electrogram SA sinoatrial node electrogram AIN anterior internodal pathway electrogram over Bachmann s bundle CS coronary sinus electrogram LA left atrial electrogram RV and LV right and left ventricular epicardial electrograms ECG limb Lead II a, atrial component, h His depolarization V ventricular component of His bundle electrogram and Cl cycle length Vertical lines are 100 msec apart

wide band AC electroencephalograph (EEG) preamplifiers and recorded on photographic film with a Midwest Optical Oscillograph (Model 591 instrumented with optical galvanometers frequency response to 3 KHz) Thus a minimum of seven local electrograms plus a Lead II electrocardiogram (ECG) were recorded in all animals The left and right thoracic vagi were carefully dissected from the mediastinal pleura between the level of the superior pulmonary veins and a point just caudal to the caudal cervical ganglia Cardiac dysrhythmias were induced by electrical stimulation (Grass Stimulator Model SD9) of the left and right thoracic vagi and their small branches [4,5,8] In nine out of 12 dogs the left thoracic small vagal nerves were stimulated prior to cervical vagotomies and in eight out of 12 dogs following cervical vagotomies. In seven out of 9 dogs the right thoracic small vagal nerves were stimulated prior to cervical vagotomies and in six out of 9 dogs following cervical vagotomies. Stimulation parameters were 20 Hz 5 msec duration 4 volts (monitored on a Hewlett Packard 120 B oscilloscope) Electrogram activation was determined by initial deflection from the isoelectric line [2]

Results

Left thoracic vagal nerves The major cardiac vagal innervation in the left thorax is via the cardiac branches of the left recurrent laryngeal nerve [4,8,11] Figs 1 and 2 illustrate the differential effects of afferent and efferent stimulation compared to efferent stimulation of a branch of this nerve In Fig 1 the first panel illustrates the control rhythm with both vagi intact The pacemaker was located functionally and/or anatomically nearest the SA nodal electrode and had a cycle length of 420 msec (heart rate 142 per minute) The AH interval of 100 msec is the time required for passage of the cardiac impulse through the A V node This value is within normal limits of 92 ± 38 msec [12,14] The HV interval of 35 msec is the time required for passage of the impulse along the Purkinje system and activation of the ventricular myocardium This HV interval is also within normal limits of 44 ± 12 msec [14,15] Note the sequential activation of the electrodes beginning with the SA node and ultimately reaching the ventricular electrodes In the second panel stimulation of an intact cardiac branch of the left recurrent laryngeal nerve increased the SA pacemaker cycle length to 830 msec (heart rate 72 per minute) while the AH and HV intervals remained at 100 and 35 msec respectively Minor alterations in sequence of activation also occurred.

In Fig 2 after left cervical vagotomy the response to identical nerve stimulation is illustrated. The SA cycle length was increased only

Direct and reflex cardiac bradydysrhythmias from small vagal nerve stimulations*

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The induction of cardiac arrhythmias particularly tachyarrhythmias by stimulation of small autonomic cardiac nerves has recently been reported [1] Bradydysrhythmias induced by vagal stimulation have been limited mainly to decentralized cervical vagal preparations and infusions of acetylcholine [3-6] These approaches eliminate the reflex effects due to stimulation of afferent fibers and generate massive vagal efferent influences on the heart which are inconsistent with traditional teachings of discrete parasympathetic activation With the recent report of cardiac afferent impulses coursing in the small vagal nerves [7,8] it is important to study both the direct efferent as well as the reflex physiologic effects of stimulation of these small nerves Using strain gauge arches recorded from selected localized myocardial segments systematic studies of the functional anatomy and regional vagosympathetic control of the canine heart have been reported [8,9] Observations concerning specific disturbances in conduction pacemaker location fixed or changing degrees of heart block and other dysrhythmias are examined in detail in this study employing local cardiac electrograms

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Methods

Acute experiments were performed on 12 mongrel dogs of either sex weighing 17 to 29 kilograms (average 22 kilograms) anesthetized with phencyclidine hydrochloride (Sernylan) 2 mg per kilogram intramuscularly, and alpha chloralose 80 mg per kilogram intravenously Positive pressure respiration was maintained with a Bird Mark 7 respirator Following bilateral thoracotomy contiguous bipolar (1 mm separation) silver electrodes were sutured onto the epicardium over the SA nodal area (SA) the area over the anterior internodal pathway (AIN) at the superior border of the interatrial septum the inferior right atrium near the ostium of the coronary sinus (CS) the left atrium (LA) and on the left and right ventricles (LV and RV) While on total cardiopulmonary bypass (10 dogs), or inflow occlusion (2 dogs) electrodes were sutured onto the endocardial surface over the area of the middle internodal pathway (MIN) at the limbus of the fossa ovalis the area of the posterior internodal pathway (PIN) between the coronary sinus and A V ring just medial to the eustacian ridge and the base of the right ventricular papillary muscle near the right bundle branch (RBB) A Hoffman type plaque electrode with five pick up points was sutured over the A V node to record the inferior atrial electrical activity His bundle electrogram (HIS) and upper ventricular septal electrical activity The shape and amplitude of the His deflection varied and depended upon electrode contact and placement [10] Sutures for all electrodes were placed parallel to cardiac fiber orientation so minimal damage occurred to the conduction pathways [2] Electrical activity was amplified with Grass Model 7P5 (1/2 ampere low frequency 0 15 Hz high frequency to 35 KHz)

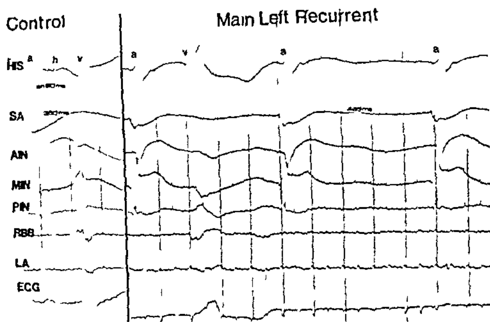


Fig 3 Direct and reflex effects of stimulation of the main left recurrent cardiac nerve MIN middle internodal pathway electrogram at limbus of the fossa ovalis PIN the posterior internodal pathway electrogram at the coronary sinus and RBB right ventricular electrogram over the right bundle branch. Other abbreviations and time lines as in Fig 1

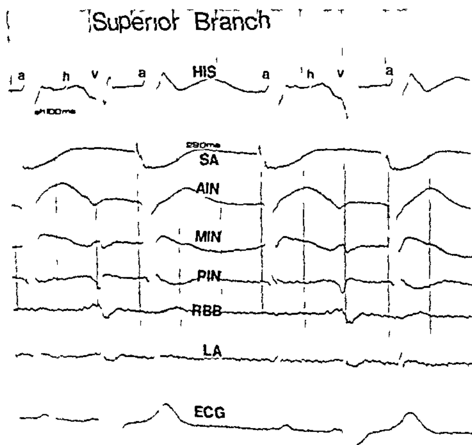


Fig 4 Direct and reflex effects of stimulation of the superior (cranial) branch of the left recurrent cardiac nerve Abbreviations and time lines as in Fig 3

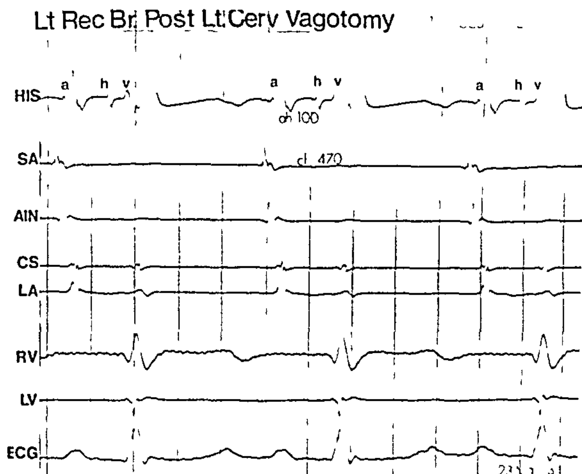


Fig 2 With the left cervical vagus sectioned, direct effects of stimulation of a branch of the left recurrent cardiac nerve Abbreviations and time lines as in Fig 1

from 420 msec to 470 msec The heart rate was decreased to 127 per minute but the AH interval remained at 100 msec. Hence only minor direct efferent innervation by this nerve to the SA pacemaker is indicated and the severe bradycardia recorded during excitation of the intact vagus was due to ipsilateral and/or contralateral reflex innervation

Branches from the left recurrent laryngeal nerve innervate the heart and electrical stimulation of these individual cardiac branches frequently induced markedly different responses Figs 3 through 6 illustrate these unique responses In Fig 3 the control cycle length was 350 msec (heart rate 171 per minute) and the pacemaker was nearest the SA nodal electrode the AH interval was 80 msec Stimulation of the main left recurrent cardiac nerve induced moderate atrial bradycardia The SA cycle length increased to 485 msec (heart rate 124 per minute) and complete heart block occurred above the bundle of His (note the absence of the h deflection) An independent slower and irregular ventricular depolarization pattern emerged

In Fig 4 stimulation of a superior (craniad) branch of the left recurrent laryngeal nerve in the same animal decreased the SA cycle length to 290 msec (acceleration in heart rate to 206 per minute) First and second degree heart block were simultaneously induced Alternate atrial impulses were blocked above the His bundle and conducted A V impulses were slowed (AH interval increased to 100 msec)

In Fig 5 stimulation of a middle branch of the left recurrent laryngeal nerve resulted in irregular atrial rhythm The pacemaker remained nearest the SA electrode but depolarized with variable frequency Atrioventricular conduction was occasional and impulse conduction was impaired (AH interval increased to 110 msec)

In Fig 6 stimulation of an inferior (caudad) branch of the left recurrent laryngeal nerve in the same animal decreased SA cycle length to 290 msec (as previously observed in the superior branch) with only slightly impaired A V conduction The AH interval increased to 100 msec while an occasional impulse was blocked above the His bundle After bilateral cervical vagotomy stimulation of the main left recurrent cardiac nerve induced third degree heart block as before but the SA cycle length decreased to 320 msec (heart rate 187 per minute) There was no

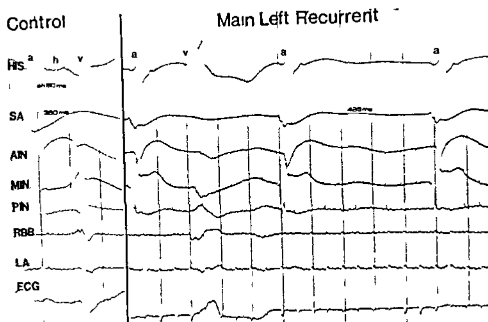


Fig 3 Direct and reflex effects of stimulation of the main left recurrent cardiac nerve MIN middle internodal pathway electrogram at limbus of the fossa ovalis PIN the posterior internodal pathway electrogram at the coronary sinus and RBB right ventricular electrogram over the right bundle branch Other abbreviations and time lines as in Fig 1

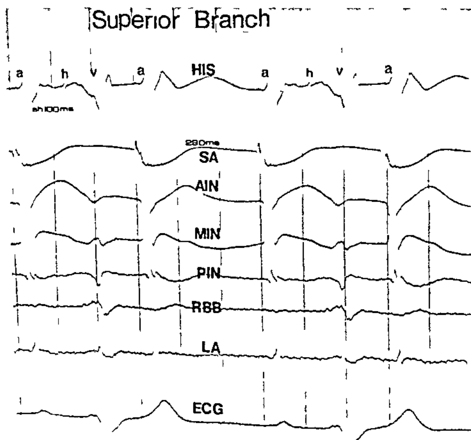


Fig 4 Direct and reflex effects of stimulation of the superior (craniad) branch of the left recurrent cardiac nerve Abbreviations and time lines as in Fig 3

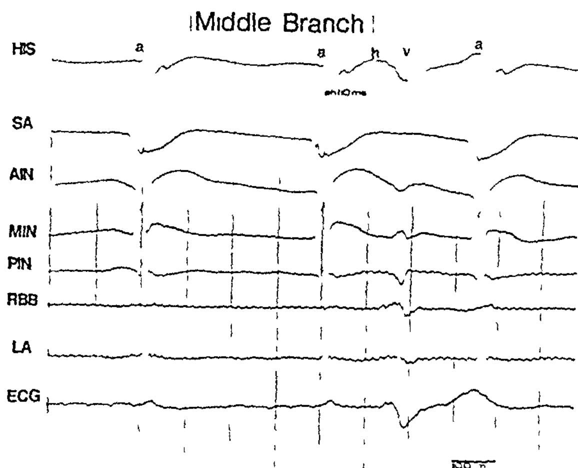


Fig 5 Direct and reflex effects of stimulation of the middle branch of the left recurrent cardiac nerve Abbreviations as in Fig 3

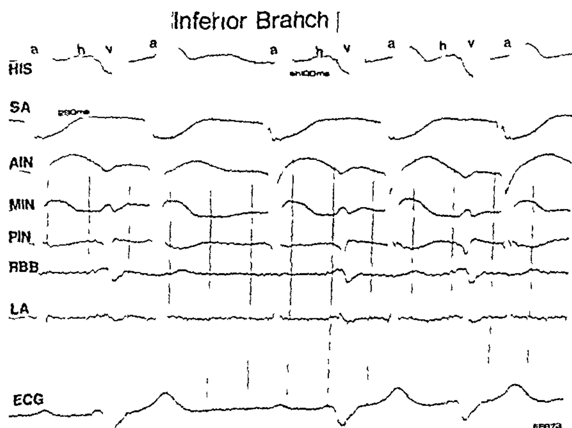


Fig 6 Direct and reflex effects of stimulation of the inferior (caudad) branch of the left recurrent cardiac nerve Abbreviations and time lines as in Fig 3

consistent number of cardiac branches from the left recurrent laryngeal nerve nor could the results of stimulating these branches be precisely predicted Such variability is probably due to varying efferent and afferent composition of the individual branches including the incorporation of sympathetic fibers

Right thoracic vagal nerves Vagal innervation of the heart from the right thorax is distributed in many nerves arising along the thoracic vagus from the caudal cervical ganglion to the level of the azygous and superior pulmonary veins[5,8,11] Figs 7 and 8 illustrate the differential effects of simultaneous afferent and efferent stimulation as compared to efferent stimulation alone (Fig 9) in two of these right vagal nerves

In Fig 7 the first panel illustrates control impulses in which the pacemaker was located nearest the MIN electrode with a cycle length of 540 msec (heart rate 111 per minute) the AH interval was 70 msec Stimulation of a small branch of the right thoracic vagus at the level of the azygous vein (right panel) induced a His bundle rhythm The first depolarization was nearest the His bundle with a cycle length of 675 msec (heart rate 89 per minute) From this point the depolarization spread retrograde to the right atrium (PIN MIN AIN SA node in sequence) and antegrade to the ventricles note that the ventricular component of the His electrogram had the same configuration as the control thereby emphasizing the superior location of the pacemaker However the His pacemaker was reflexly induced since right cervical vagotomy eliminated the His pattern The precise distribution of the efferent innervation to the His bundle is not definitely established but stimulation of the left ventral lateral cardiac nerve has been shown often to induce a His pacemaker tachydysrhythmia[2] There were no measurable efferent effects when this small nerve was stimulated after cervical vagotomy thus amplifying the fact that it carried predominantly afferent fibers.

In Fig 8 the oscillograph tracings are as in Fig 1 The control rhythm had a cycle length of 480 msec (heart rate 125 per minute) and the pacemaker was located nearest the SA nodal electrode with an AH interval of 95 msec Stimulation of a major branch of the right thoracic vagus a branch located 4 cm distal to the caudal cervical ganglion induced virtual cardiac asystole with left cervical vagus either intact or sectioned. There was only one escape beat during the 15 second stimulation and it is shown in the middle panel From analysis of the ventricular electrograms (RV before LV) the widened QRS of the electrocardiogram and the inverted His depolarization it is postulated that this lone escape beat originated in the right bundle branch This ventricular escape impulse coursed cranіad and depolarized the right atrium in a caudad to craniad direction

In the right panel of Fig 8 stimulation of this same right vagal branch after right cervical vagotomy then resulted in SA nodal bradycardia with a cycle length of 810 msec (heart rate 74 per minute) The AH interval was only slightly shortened, indicating no depression of A V nodal conduction

Since virtual cardiac asystole was induced by both direct efferent stimulation of this right vagal branch and ipsilateral reflexes stimulation of the distal end of the right cervical vagus was also expected to induce virtual cardiac asystole However in Fig 9 this stimulation actually resulted in an impulse originating close to the coronary sinus electrode with increased A V nodal conduction rate (AH interval 85 msec) This was followed by an impulse with altered pacemaker location (AIN) depressed A V nodal conduction (AH interval 175 msec) and prolonged HV interval (140 msec.) The ventricular electrograms again indicated right bundle branch escape A final coronary sinus impulse occurred with complete heart block above the His bundle This was followed by a 2 5 second period of asystole with a right bundle branch escape as previously observed except for minor atrial activation changes.

In Fig 10 the electrograms were recorded after bilateral cervical vagotomies and during stimulation of the right thoracic vagus at a point distal to the caudal cervical ganglion Cardiac asystole was induced early in the stimulation until this group of impulses developed near the end of the stimulation The first depolarization sequence arose from a pacemaker nearest the SA electrode the AH interval was 90 msec The second atrial depolarization originated 175 msec later this time from near the AIN electrode but was blocked in the A V node above the His bundle The final atrial impulse again arose near the AIN electrode with an AH interval of 140 msec The left ventricular electrogram preceded the

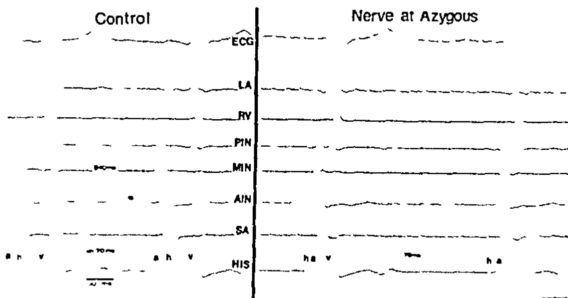


Fig 7 Reflexly induced His bundle bradydysrhythmia with stimulation of a right vagal cardiac nerve Abbreviations as in Fig 3

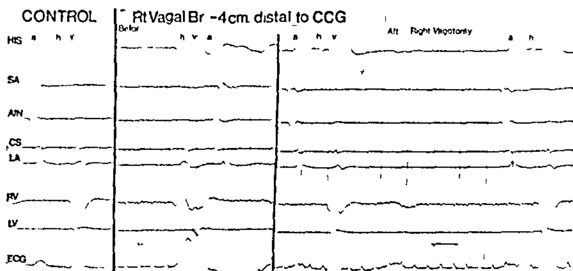


Fig 8 Direct and ipsilateral reflex effects of stimulation of a right vagal cardiac nerve Abbreviations as in Fig 1

right ventricular electrogram by 50 msec indicating partial right bundle branch blockade A long period of asystole followed.

The bottom half of this figure demonstrates a second series of rapid depolarizations 800 msec after the vagal stimulation was terminated The first impulse arose nearest the SA electrode the AH interval was 90 msec The second impulse originated nearest the AIN electrode and was blocked above the His bundle The third impulse arose nearest the AIN electrode and the AH interval was normal Partial right bundle branch blockade was indicated in the electrocardiogram and ventricular electrograms After a 500 msec. period of atrial asystole a normal SA nodal rhythm resumed (cycle length 500 msec , AH interval, 90 msec)

Discussion

The autonomic nervous system is known to be involved in the genesis of many arrhythmias Recent work has been concerned primarily with tachyarrhythmias induced by stimulation of efferent sympathetic nerves to the heart [1,2] However in recent reports concerned primarily with vagal control of localized cardiac inotropism various degrees of heart block and arrhythmia in response to direct and reflex vagal activation were noted [8,9] This study more carefully examines these cardiac bradydysrhythmias using multiple cardiac electrograms

Previous studies have indicated that the left efferent vagus generally innervates the A V node while the right efferent vagus generally innervates the SA node [3,5,16] In this study the direct

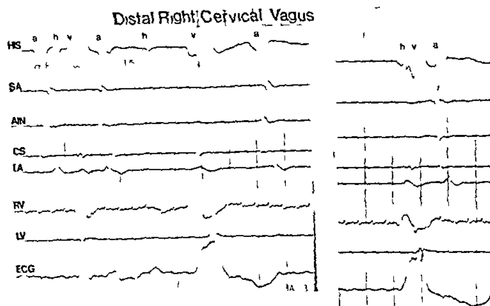


Fig 9 Cardiac asystole with escape impulse during stimulation of the distal right cervical vagosympathetic trunk. Abbreviations and time lines as in Fig 1

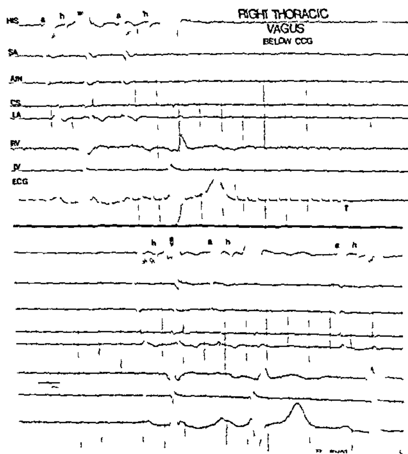


Fig 10 Supraventricular vagal escape bursts during stimulation of the right distal thoracic vagosympathetic trunk. Abbreviations as in Fig 1

and reflex induced cardiac bradydysrhythmias reveal the diffuse cardiac innervation by small individual vagal branches In general the left thoracic vagal fibers course onto the heart in the cardiac branches of the left recurrent laryngeal nerve Stimulation of the vagal fibers and the left thoracic vagus distal to the origin of recurrent cardiac nerves elicit little or no direct or reflex effects on cardiac parameters which were monitored Stimulation of the left thoracic vagus cranial to the origin of the recurrent cardiac nerve after the recurrent cardiac nerve is severed usually elicits only contralateral reflex effects (bradycardia) These observations confirm the major vagal route to the heart in the left thorax to be the recurrent cardiac nerve and its branches In addition the results in this study tend to confirm earlier patterns that is the left efferent vagal innervation to the A V node and the right vagal innervation to the SA node [3,5,16] These patterns however, are not absolute and on occasion left recurrent cardiac nerve stimulation would reflexly (Fig 1) and directly depress the SA node (Fig 2) This demonstration of a cardiocardiac vagal reflex is consistent with both experimental and clinical observations [9,17,18] The left recurrent cardiac nerve directly inhibited A V nodal conduction in all but one experiment (Figs 1 and 2) The intensity of A V nodal depression was determined by the individual fiber or branch of the left recurrent nerve which was stimulated First degree heart block (Fig 6) second degree heart block (Fig 4) and third degree block (Fig 3) were all directly induced by individual stimulations of branches of the recurrent cardiac nerve

Heart rate effects produced by left recurrent cardiac nerve stimulations were variable Generally bradycardia was induced (Figs 1 through 3) however slight tachycardia could also be elicited by stimulation of branches of the left recurrent nerve (Figs 4 through 6) The mechanism of this tachycardia is unknown but it is probably due to false reciprocal excitation that is due to stimulation of sympathetic fibers in the left recurrent cardiac nerves [19] Propranolol was not administered in any of these experiments to separate sympathetic adrenergic from parasympathetic cholinergic effects The degree of direct or reflex bradycardia and/or the amount of A V node depression induced by each of the left recurrent cardiac branches was not sufficiently consistent for statistical analysis

In the right thorax cardiac vagal innervation has no single major route but courses in many fibers arising from near the right caudal cervical ganglion caudally to the azygous vein and superior pulmonary vein These fibers have been generally grouped into cranio and caudovagal fibers along with the right recurrent cardiac nerve [5]

Stimulation of the individual right thoracic cardiac vagal fibers seldom depressed A V nodal conduction When this A V conduction depression did occur with right vagal nerve stimulation it could be abolished by cervical vagal sectioning which eliminated the reflex routes of its induction Similarly the establishment of His bundle rhythms with stimulation of right vagal nerves was generally reflexly mediated (Fig 7) The mechanism for the establishment of the His bundle bradydysrhythmia was probably due to selective inhibition of supraventricular pacemakers since left sympathetic mediated His bundle pacemakers result in tachydysrhythmias [2]

The greatest effects of right vagal nerve stimulation were upon heart rate These effects were both direct and reflexly mediated. The reflex effects upon the SA node were ipsilateral that is, both afferent and efferent pathways were in the right vagus It must be noted that cervical vagus sectioning does not eliminate vagovagal reflexes or even vagosympathetic reflexes which may be mediated in the peripheral ganglia In this study these local reflexes if present would be interpreted as direct efferent innervation effects.

That these heart rate effects produced by right vagal nerve stimulation were both direct and reflexly mediated is illustrated in Fig 8 The direct efferent bradycardia is severe but not nearly as complete as the total asystole evoked with the direct and reflex effects Duplication or simulation of the direct and ipsilateral reflexly induced asystole can be accomplished Fig 9 illustrates that stimulation of the distal right cervical vagus will activate the direct and reflex pathways and therefore reproduce the asystole with right bundle branch escape seen in Fig 8 However the development of an asystolic condition in Fig 9 requires time for generation of three right atrial impulses from non SA nodal sites These impulses were conceivably elicited by stimulation of sympathetic fibers coursing in the vagus nerve [19] Their excitation may result in minor increased automaticity in cells near the CS and AIN electrodes thus delaying the asystole

Such sympathetic fibers would not be expected to have been activated in the reflexly induced asystole

The functional location of the cardiac pacemaker is known to be influenced by the autonomic nervous system[2,20,21] Pacemaker location during control states was frequently but not exclusively in the SA node An example of a MIN pacemaker during control was observed in the present report (Fig 7) and shifts in location during both direct and reflex vagal stimulation were observed (Figs 8 and 10)

When supraventricular pacemaker escape occurred during cervical vagal stimulation it was often characterized by rapid, successive depolarizations (Fig 10) The rapid depolarization sequences may have been due to increased automaticity of cells near the AIN electrode and due to the conduction disturbances (decreased conductivity and conduction blocks) from vagally released acetylcholine a re entrant circuit was established This circuit however was not monitored by our electrodes Conditions favoring re entry (one way entrance block and slow conduction[22]) are likely to occur in the presence of highly localized vagally released acetylcholine The indications of right bundle branch blockade with vagal stimulation are consistent with other reports of depressed Purkinje conduction during acetylcholine infusion[17] However these instances of apparent vagal innervation of the bundle branches may only be the end result of selective vagal alteration of A V node activation and/or conduction

Summary

Alterations in cardiac pacemaker location its rate of discharge and A V conduction patterns were induced in anesthetized adult dogs by electrical stimulation of the thoracic vagi and their small cardiac branches before and after cervical vagotomy Electrical activity from small, contiguous bipolar silver electrodes was amplified and recorded by an optical oscillograph The electrodes were located over the SA node the three internodal pathways the left atrium and ventricular epicardium. A Hoffman type plaque electrode was placed over the A V node to record a His bundle electrogram simultaneously with a Lead II electrocardiogram Electrical stimulation of the intact left recurrent laryngeal nerve and its cardiac branches before and after vagotomy induced both direct and reflex effects on SA nodal cycle length Efferent dromotropic effects on the A V node varied from first to third degree heart block during stimulation of individual left recurrent cardiac branches Stimulation of the right recurrent cardiac nerve induced atrial bradycardia with heart block above the His bundle Stimulation of individual right vagal branches near the heart induced bradycardia cardiac asystole shifts in atrial pacemaker location or activation of His pacemakers Establishment of the His rhythm probably indicates selective inhibition of supraventricular pacemakers but not of the His bundle Asystole and His rhythms induced during stimulation of the more caudal branches of the right cardiac vagal nerves were generally reflexly mediated and were abolished by cervical vagotomy

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The hıgh frequency electrocardıogram ın coronary artery dısease

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At the Chelsea Clınıcal Socıety ın 1912 Eınthoven stated ıf the movements of the strıng could be made 10 or 100 tımes faster the sensıtıveness remaınıng the same or even ıf theoretıcally spoken an ınstrument were available wıth an ınfınıtely small deflectıon tıme the form and dımensıons of the recorded EKG s would not be thereby perceptıbly changed [1] Whıle fıne notchıng of the QRS complex was noted early ın the hıstory of electrocardıography [2] Eınthoven s statement was not challenged untıl 1933 when Reıd and Caldwell[3] showed that the one hundredth harmonıc of the electrocardıogram (ECG) was larger than the fundamental Langner and co workers[4 5] then developed the technıques for demonstratıng hıgh frequency components ın the electrocardıogram by expandıng the frequency response of the ECG and dısplayıng the QRS complexes at more rapıd paper speeds Subsequent reports by Langner and co workers[6 10] and others[11 14] emphasızed the ıncreased ıncıdence of hıgh frequency notchıng and slurrıng ın the QRS complexes of patıents wıth coronary artery dısease

Correlatıons between hıgh frequency components and anatomıc fındıngs have shown that fıbrosıs ıs assocıated wıth or a cause of hıgh frequency components [2 7 13 14]

Thıs study was undertaken to determıne the dıagnostıc sıgnıfıcance of hıgh frequency components ın the electrocardıogram of patıents wıth coronary artery dısease wıth and wıthout documented myocardıal ınfarctıon Second we attempted to establısh correlatıons between hıgh frequency notchıng and coronary cıneangıographıc fındıngs and the maxımal treadmıll exercıse test

Methods

The hıgh frequency ECG was obtaıned by expandıng the frequency response of the electrocardıograph to 1 200 Hz and obtaınıng the fırst derıvatıve of thıs sıgnal as descrıbed by Langner and co workers [15 16] QRS complexes of the standard 12 leads and bıpolar paraorthogonal Leads X, Y and Z* were dısplayed wıth theır respectıve derıvatıves on a Tektronıx 564 oscılloscope and photographed wıth a Polaroıd C 12 camera The tracıngs were recorded at 500 mm per second. Standardızatıon was accomplıshed by ıntroducıng a 0 5 mV trapezoıdal pulse ınto the electrocardıographıc amplıfıer whıch resulted ın a 2 cm deflectıon of the ECG on the oscılloscope The leadıng edge of the trapezoıdal pulse had a rıse tıme of 125 mV per second whıch provıded the standardızatıon for the fırst derıvatıve producıng a 1 cm deflectıon ın derıvatıve amplıtude After recordıng the hıgh frequency ECG notchıng and slurrıng of the QRS complex was counted as descrıbed by Langner and assocıates [10 15 16] Brıefly a notch ıs defıned as a major change ın the dırectıon of the QRS complex excludıng dırectıonal changes occurrıng at the peak of the R wave or nadır of the S wave The correspondıng derıvatıve of a notch changes sıgn or passes through zero A slur ıs a

*See ref en e 12 Fig *

From th Kra ert Inst tute of Ca d ology Marı n County General Hosp tal, nd the Depa tm t of Med cıne Indıana Unıve sıty School of Medı ıne Indı n pol s.

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Reprı t requests Dr Gary J Anderson The H hn man Medı al College & Hospital of Ph lad lph a D partment f Card logy 230 N Broad St., Phıladelphı P 19102.

Table I Comparison of notching in normals (Group I), patients with angina pectoris (Group II) and myocardial infarction (Group III) Values for notching are the mean ± S E Below the notch count, the per cent of patients having an abnormal lead (> 2 S D for notching) are given The mean value of notching is significantly different from the value of the control group

		I	II	III	aV_R	aV_L	aV_F
Group I (N = 109)	Notches	0 9 ± 1 2	1 3 ± 1 3	3 4 ± 1 8	0 4 ± 0 7	2 2 ± 1 7	2 6 ± 1 8
	per cent abnormal	4 6	2 8	1 8	73 4	3 7	1 8
Group II (N = 36)	Notches	0 7 ± 1 1	1 9 ± 1 9	3 7 ± 2 8	0 7 ± 1 0	1 9 ± 1 9	3 1 ± 2 0
	per cent abnormal	3 0	9 1	6 1	9 1	6 1	3 0
	Significance	NS	NS	NS	NS	NS	NS
Group III (N = 58)	Notches	2 0 ± 2 5	2 7 ± 2 6	4 2 ± 3 0	1 9 ± 2 1	3 5 ± 2 5	4 7 ± 3 4
	per cent abnormal	10 2	20 4	14 3	44 9	20 4	22 5
	Significance	0 01	0 01	NS	0 01	0 01	0 01
		V_1	V_2	V_3	V_4	V_5	V_6
Group I (N = 109)	Notches	2 4 ± 1 5	1 9 ± 1 4	1 7 ± 1 4	0 7 ± 0 8	0 4 ± 0 7	0 3 ± 0 6
	per cent abnormal	1 8	4 6	3 7	5 5	7 3	7 3
Group II (N = 36)	Notches	2 1 ± 1 8	1 9 ± 2 0	1 5 ± 1 4	1 0 ± 1 1	0 7 ± 0 8	1 0 ± 1 4
	per cent abnormal	6 1	6 1	6 1	9 1	15 2	24 2
	Significance	NS	NS	NS	NS	NS	0 05
Group III (N = 58)	Notches	2 9 ± 2 2	3 1 ± 3 4	4 1 ± 4 9	3 8 ± 5 1	2 6 ± 2 8	2 1 ± 2 8
	per cent abnormal	22 5	22 5	30 0	46 9	46 9	36 7
	Significance	NS	NS	0 01	0 01	0 01	0 01
		X	Y	Z			
Group I (N = 109)	Notches	0 6 ± 0 8	3 2 ± 2 1	2 8 ± 2 1			
	per cent abnormal	2 8	4 6	5 5			
Group II (N = 36)	Notches	0 8 ± 1 0	3 7 ± 2 1	1 8 ± 1 9			
	per cent abnormal	9 1	6 1	3 0			
	Significance	NS	NS	(0 05)			
Group III (N = 58)	Notches	2 2 ± 2 6	4 2 ± 3 6	3 4 ± 4 6			
	per cent abnormal	32 7	14 3	4 1			
	Significance	0 01	NS	NS			

Negative correlation

deflection in the QRS complex in which the corresponding derivative does not pass through zero

The control group (Group I) was composed of 109 state policemen followed annually with history physical examination chest x ray, conventional ECG and maximal treadmill exercise test These patients were free from known heart disease or other diseases known to affect the myocardium Group II was composed of patients having the clinical diagnosis of angina pectoris and free from associated diseases known to involve the myocardium In addition patients with documented hypertension were excluded from the study Group III was composed of 49 patients with myocardial infarction (MI) documented by history, serum enzyme changes and ECG criteria for MI Group IIIa was composed of patients having MI by history, but without ECG criteria for myocardial infarction at the time of study Documentation of antecedent MI in Group IIIa was established by a positive history, documentation of serial enzyme changes and ECGs obtained at the time of hospitalization for the acute MI

Coronary arteriographic studies were performed by selective opacification of each coronary artery by hand injections of Renografin 76 or 75 per cent Hypaque through a catheter percutaneously introduced into the femoral artery Cineangiographic studies were recorded on Eastman Double X negative film at 64 frames per second The coronary cinearteriograms were reviewed by three physicians for purposes of grading the degree of stenosis of the major coronary arteries and their branches The technique and criteria for evaluation of the maximal treadmill exercise test have been described elsewhere [17]

Statistical analyses were performed by the Indiana University—Purdue University Indianapolis Research Computer Center Statistical sig

Table II Total number of abnormal leads in each group

		No of abnormal leads											
		0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Group I	N = 109	68	25	5	8	3							
	%	62 4	22 9	4 6	7 3	2 8							
Group II	N = 36	14	10	6	1	2							
	%	38 9	30 3	18 2	3 0	6 1							
Group III	N = 58	6	12	2	8	7	7	5	4	2	1	2	2
	%	10 3	20 7	3 4	13 8	12 1	12 1	8 6	6 9	3 4	1 7	3 4	3 4

Table III Analysis of age sum of notching and number of abnormal leads for each group

	No	*Age (years)*	*Notches (mean ± SE)*	*Abnormal leads (mean ± SE)*
Group I	109	37 9 ± 8 3	22 2 ± 17 8	0 7 ± 3 4
Group II	36	54 9 ± 12 2	23 3 ± 12 9	1 0 ± 3 0
Group III	58	56 6 ± 13 3	44 6 ± 10 7	3 7 ± 7 3
Group IIIa	13	51 3 ± 14 2	70 5 ± 21 0	3 5 ± 0 5

nificances were determined utilizing the Student s t test Notches were counted and the mean values were established for each lead and respective group An abnormal notch count was defined as a notch count which exceeded two standard deviations In this text the term abnormal lead refers to notch counts which were greater than two standard deviations from the mean value The total notch count for a patient was derived by summing the notch count for each of the 12 standard and three bipolar paraorthogonal leads

Results

Group I was composed of 109 patients without evidence of heart disease The mean age was 37 9 ± 8 3 years Notching of the QRS complex was least common in limb Leads I II aV_R the lateral precordial Leads V_4 V_5 and paraorthogonal Lead X (see Table I) Abnormal leads based upon notch count were observed in 41 patients (37 6 per cent) and 97 2 per cent of the patients had three or less abnormal leads (Table II) In Group I Leads aV_R V_5 and V_6 had the least frequent notch count followed by paraorthogonal Lead X and Lead I Paraorthogonal Lead Y demonstrated high notch counts in which the notching was most prominent in the downstroke of the R wave

Group II was composed of patients having a clinical history consistent with the diagnosis of angina pectoris The mean age was 54 9 ± 12 2 years (see Table III) The mean total notch count was 23 3 ± 12 9 compared with 22 2 ± 17 8 for Group I (p > 0 5) Although the total notch count failed to differentiate Group II patients from the normal group single lead analysis showed a higher notch count in Lead V_6 (p < 0 05) and a lower notch count in paraorthogonal Lead Z (see Table I) Fifteen per cent of the patients in Group II had an abnormal notch count in Lead V_5 and 24 per cent showed an abnormal notch count in Lead V_6 A higher incidence of notching was also observed in Leads II V_4 and X although the differences were not significant. We were unable to establish that slurring was significantly different between Groups I and II (see Table IV) In Group II 30 3 per cent of the patients had one abnormal lead based on notch count 18 2 per cent had two abnormal leads and 9 1 per cent had three or more abnormal leads (see Table II) Thus 57 6 per cent of Group II patients had one or more abnormal leads compared with 37 4 per cent of Group I patients The higher incidence of single lead abnormality was primarily a result of the increased frequency of lateral precordial leads having abnormally high notch counts

Group III (see Table III) was composed of patients with an established diagnosis of MI The mean age was 56 6 ± 13 3 years The sum of the notching in the 15 leads was 44 6 ± 10 7 and was

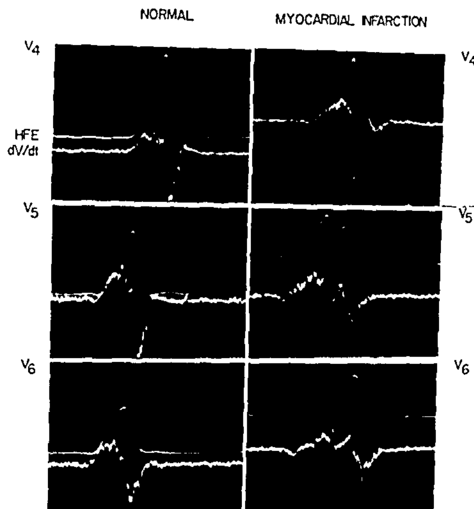


Fig 1 High frequency electrocardiograms (HFE) obtained from a normal patient (left column) and a patient with documented inferior wall infarction (right column) The first derivative (dV/dt) is displayed with each QRS complex Leads V_5 and V_6 in the infarcted heart show an abnormal contour of the QRS complexes compared with the normally smooth contour of Leads V_5 and V_6 (left)

significantly different from Group I and II ($p < 0.01$ level see Table IV) Eighty eight per cent of the patients had at least one abnormal lead based on notch count and 49 per cent showed four or more abnormal leads The anterior and lateral precordial leads were most frequently ab normal as were paraorthogonal Leads X and aV_R Tables I and IV show those leads capable of dif ferentiating Group III from Group I patients Slurring of the QRS complex was significant in Leads V_5 and X ($p < 0.01$) and AV_R and V_6 ($p < 0.05$)

Notching did not correlate with the presence of abnormal Q waves (defined as > 0 04 second or > 25 per cent the height of the R wave) in any given lead For instance seven patients had ab normal Q waves in Leads II III and aV_F and yet demonstrated normal notch counts in these leads Of these seven patients four had abnormal notch counts in Lead aV_R six had abnormal lateral precordial leads and two had abnormal paraorthogonal Lead X Fig 1 represents one such example For illustrative purposes we have mounted normal QRS complexes and the respec tive derivatives of Leads V_4 V_5 and V_6 to the left of Leads V_4 V_5 and V_6 obtained from a patient with a documented inferior wall MI Precordial Lead V_4 is not significantly different from normal and contains one notch on the terminal down stroke Lead V_5 has an unusual morphology with two peaks separated by a low frequency notch and is abnormal ($p < 0.05$) Lead V_6 while visually having an unusual morphology is statistically normal based on notch count Coronary cinean giography revealed 100 per cent obstruction of the right coronary artery 50 per cent obstruction of the left anterior descending artery, and a nor mal left main and left circumflex artery

Correlation between arteriographic findings and the high frequency electrocardiogram Our

Table IV Significance of notching and slurring between groups

Groups	Notching		Slurring	
	P<0 01	P<0 05	P<0 01	P<0 05
I vs II	No significant leads	V_6 Z	No significant leads	No significant leads
I vs III	I II aV_R aV_L aV_F V_3 V_4 V_5 V_6 X (Total)	No significant leads	V_5 X	aV_R V_6
II vs III	X, I aV_R aV_L V_3 V_4 V_5 (Total)	Z, aV_F, V_6	No significant leads	X, V_6

Group I, normal subjects (No = 109) Group II angina pectoris (N = 36) and Group III myocardial infarction (No = 58)
Negative correlation

Table V Per cent of patients having an abnormal lead correlated against 75 per cent or greater obstruction of the respective vessel

	I	II	III	aV_R	aV_L	aV_F
LAD (18)	11 1	27 8	16 7	61 1	27 8	38 9
RCA (19)	10 5	31 6	21 1	68 4	31 6	36 8
LCA (13)	15 4	23 1	15 4	53 8	23 1	30 8

	V_1	V_2	V_3	V_4	V_5	V_6	X	Y	Z
LAD (18)	5 6	33 3	38 9	66 7	66 7	50 0	50 0	16 7	0
RCA (19)	5 3	21 1	42 1	63 2	63 2	47 4	47 4	21 1	0
LCA (13)	0	15 4	30 8	30.8	53 8	30 8	30 8	15 4	0

data showed that notching could separate patients in Group III from normal patients As stated above we observed that not infrequently the abnormal lead (based either on notching or less frequently slurring) did not correspond to the lead having abnormal Q waves We then attempted to correlate the presence of abnormal high frequency components with significant obstruction (defined as ≥ 75 per cent) of one or more coronary arteries demonstrated on coronary cineangiograms Table V shows the per cent of patients having an abnormal specific lead associated with significant obstruction of the indicated coronary artery It would be expected that lesions of the right coronary artery would be associated with abnormalities of the inferior wall leads and lesions of the LAD would be reflected by a higher incidence of high frequency components in the anterior wall leads and so forth When patients were divided into groups according to artery involvement no significant differences were observed between groups Patients with 75 per cent or greater obstruction of the left anterior descending (LAD) artery had a similar incidence of abnormalities of anterior wall leads as did patients with lesions of the right coronary or circumflex arteries. Precordial Leads V_2 and V_6 were more frequently abnormal in patients with significant obstruction of the LAD artery However Leads V_3 V_4 and V_5 were no different in this group than in the other groups This observation may result from the fact that in nearly all cases an obstruction of one vessel (≥ 75 per cent) was often associated with involvement of additional vessels For this reason lesions of the LAD might not be expected to demonstrate a high incidence of abnormal high frequency components only in the anterior precordial leads For instance patients in the RCA group might have additional significant obstruction of the LAD

Since multiple vessel involvement would tend to obscure correlations between vessel obstruction and a corresponding abnormal lead we analyzed the data individually rather than as a

Table VI Abnormal leads correlated with coronary cineangiographic findings

		> 75% occlusion				Lead								
	Study No.	*RC*	*LM*	*LAD*	*LC*	*I*	*II*	*III*	aV_R	aV_L	aV_F	V_1	V_2	V_3
Group II	32	100		75										
	63	75		100										
	208			100										
	248		75											
	296			75										
	302			75								X		
	350			75					X					
	352				100					X				
	364			75										
	No	2	1	7	1	0	0	0	1	1	0	1	0	0
	Per cent	22 2	11 1	77 8	11 1	0	0	0	11 1	11 1	0	11 1	0	0
Group III	65	100			75				X					X
	114			100			X		X					
	183			100	75									
	193			100					X					
	285	75			100		X	X	X	X	X		X	
	295			100	100			X						X
	303	100		75							X			
	317	75												
	320	100		100						X			X	X
	323	100		75									X	X
	331	100		100					X	X	X			X
	336	75		100		X	X		X	X	X		X	X
	338	75		100		X	X		X	X	X			
	347	100			75									X
	354	100			100				X					
	357			100					X				X	
	361	75					X		X					
	362	100		75				X						X
	367	100							X					
	372		100									X		
	379			100	100				X		X			
	380	75		100	100				X					
	381	100					X	X		X	X	X		
	384			100									X	
	389			100										
	390	75		100	75				X					
	No	17	1	17	9	2	6	4	14	6	7	2	6	8
	Per cent	65 4	3 8	65 4	34 6	7 7	23 1	15 4	53 8	23 1	26 9	7 7	23 1	30 8

group (see Table VI) Several patients in Group II demonstrated predominant single vessel disease (Study No 302 352 and 364) Study 302 indicates that the patient had abnormal Leads V_1 V_5 and V_6 and cineangiographically demonstrated 75 per cent obstruction of the LAD artery The presence of three abnormal anterior and lateral wall leads suggested involvement of the left anterior descending artery However, Cases 354 and 364 had only one abnormal lead and could not have been separated from the normal group

The ability to predict an abnormally high notch count lead from the angiograms of patients in Group III was poor Sixty five per cent of the patients had 75 per cent or more obstruction of the right coronary artery yet the incidence of abnormalities of the inferior wall leads was relatively low In this group the incidence of abnormalities of Leads II, III, and aV_F was 23 1 per cent 15 4 per cent and 26 9 per cent, respectively The number of patients in Group III with isolated lesions of the right coronary artery was

…	V_4	V_5	V_6	X	Y	Z	No abnormal leads
							0
							0
					X		1
							0
							0
		X	X				3
							1
			X				2
	X						1
	1	1	2	0	1	0	
	11 1	11 1	22 2	0	11 1	0	
	X	X	X	X			6
	X		X				4
							0
	X			X			3
	X	X	X	X	X		11
	X	X					4
	X			X	X		4
							0
		X	X		X		6
		X	X	X			5
	X	X		X			7
	X	X		X			10
	X	X					7
							1
							1
	X	X	X	X			6
	X		X	X			5
	X	X	X				5
							1
							1
		X	X				4
	X	X	X				4
		X					6
	X						2
				X			1
							1
	14	13	10	10	3		
	53 8	50 0	38 5	38 5	11.5		

insufficient to make any conclusions referable to the diagnostic specificity of notching in the inferior wall leads Case 381 (Table VI) represents a case with inferior wall infarction in which six leads (Leads II III aV_L aV_F, V_1 and V_6) were observed to have abnormally high notch counts. On coronary cineangiography 100 per cent obstruction of the right coronary artery was observed However no lesions of the remainder of the coronary arterial system could account for the notching in Leads V_1 or aV_L and V_6 Of the 49 patients in Group III we were able to identify 13 patients (Group IIIa) who failed to have conventional ECG s which were diagnostic of MI The data referable to these patients are presented in Table VII Patients in Group IIIa were younger than in Group III as a whole 51 3 ± 14 2 years vs 56 6 ± 13 3 years respectively The sum of the notching in the 15 leads was higher in Group IIIa having 71 ± 21 notches per high frequency ECG compared with 44 6 ± 10 7 for Group III as a whole Despite the higher sum of the notch count the incidence of abnormally notched leads was 3 5 ± 0 5 no different from Group III having 3 7 ± 7 3 Nonetheless those patients having clinically documented MI but only nonspecific changes on the conventional ECG could not be differentiated as a group from those patients having MI with conventional ECG s diagnostic of infarct patterns

Notch count and treadmill exercise test Fig 2 shows the data in which the total notch count was correlated with the treadmill maximal exercise test In the anginal group no significant differences were observed in notch count in the subgroups having negative equivocal or positive exercise tests Similarly in Group III statistically significant differences were not observed between subgroups although the total notch count was higher in those patients having equivocal exercise tests (54 8 ± 2 8) compared with those having a negative exercise test (43 1 ± 9 5)

Discussion

This study confirms the previous observations that the high frequency ECG is abnormal in the presence of MI Furthermore the high frequency ECG remains abnormal when the conventional ECG fails to show electrocardiographic criteria for MI A previous experimental report[7] showed that the high frequency ECG may remain abnormal in the presence of MI without the development of Q waves In that study focal necrosis was induced by the injection of formalin into the left ventricular muscle The resulting necrosis was insufficient to induce transmural injury and Q waves were not observed, although the high frequency ECG showed the development of fine notching and slurring of the QRS complex We have confirmed this observation in 13 patients with documented MI whose conventional ECG s have failed to indicate the presence of an old MI

Table VI Abnormal leads correlated with coronary cineangiographic findings

Study No		> 75% occlusion				Lead								
		RC	LM	LAD	LC	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3
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	63	75		100										
	208			100										
	248		75											
	296			75										
	302			75								X		
	350			75					X					
	352				100					X				
	364			75										
	No	2	1	7	1	0	0	0	1	1	0	1	0	0
	Per cent	22 2	11 1	77 8	11 1	0	0	0	11 1	11 1	0	11 1	0	0
Group III	55	100			75				X					X
	114			100			X		X					
	183			100	75									
	193			100					X					
	285	75			100		X	X	X	X	X		X	
	295			100	100			X						X
	303	100		75							X			
	317	75												
	320	100		100						X			X	X
	323	100		75									X	X
	331	100		100					X	X	X			X
	336	75		100		X	X		X	X	X		X	X
	338	75		100		X	X		X	X	X			
	347	100			75									X
	354	100			100				X					
	357			100					X				X	
	361	75					X		X					
	362	100		75				X						X
	367	100							X					
	372		100									X		
	379			100	100				X		X			
	380	75		100	100				X					
	381	100					X	X		X	X	X		
	384			100									X	
	389			100										
	390	75		100	75				X					
	No	17	1	17	9	2	6	4	14	6	7	2	6	8
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group (see Table VI) Several patients in Group II demonstrated predominant single vessel disease (Study No 302 352, and 364) Study 302 indicates that the patient had abnormal Leads V_1 V_5 and V_6 and cineangiographically demonstrated 75 per cent obstruction of the LAD artery The presence of three abnormal anterior and lateral wall leads suggested involvement of the left anterior descending artery However, Cases 354 and 364 had only one abnormal lead and could not have been separated from the normal group

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V_4	V_5	V_6	X	Y	Z	No. abnormal leads
						0
						0
				X		1
						0
						0
	X	X				3
						1
		X				2
X						1
1	1	2	0	1	0	
11 1	11 1	22.2	0	11 1	0	
X	X	X	X			6
X		X				4
						0
X			X			3
X	X	X	X	X		11
X	X					4
X			X	X		4
						0
	X	X		X		6
	X	X	X			5
X	X		X			7
X	X		X			10
X	X					7
						1
						1
X	X	X	X			6
X		X	X			5
X	X	X				5
						1
						1
	X	X				4
X	X	X				4
	X					6
X						2
			X			1
						1
14	13	10	10	3		
53 8	[illegible]0 0	38 5	38 5	11.5		

insufficient to make any conclusions referable to the diagnostic specificity of notching in the inferior wall leads Case 381 (Table VI) represents a case with inferior wall infarction in which six leads (Leads II III aV$_L$, aV$_F$, V$_1$ and V$_5$) were observed to have abnormally high notch counts On coronary cineangiography 100 per cent obstruction of the right coronary artery was observed. However no lesions of the remainder of the coronary arterial system could account for the notching in Leads V$_1$ or aV$_L$ and V$_5$ Of the 49 patients in Group III we were able to identify 13 patients (Group IIIa) who failed to have conventional ECG s which were diagnostic of MI The data referable to these patients are presented in Table VII Patients in Group IIIa were younger than in Group III as a whole, 51 3 ± 14 2 years vs 56 6 ± 13 3 years respectively The sum of the notching in the 15 leads was higher in Group IIIa having 71 ± 21 notches per high frequency ECG compared with 44 6 ± 10 7 for Group III as a whole Despite the higher sum of the notch count the incidence of abnormally notched leads was 3 5 ± 0 5 no different from Group III having 3 7 ± 7 3 Nonetheless those patients having clinically documented MI but only nonspecific changes on the conventional ECG could not be differentiated as a group from those patients having MI with conventional ECG s diagnostic of infarct patterns

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Table VII Clinical coronary cineangiographic and abnormal lead data obtained from Group IIIa

Study No	Age	Sex	Age MI (years)	Abnormal leads	Cine			Total notches
					RCA	LAD	LCA	
A 367	49	M	1	aV_R	0	50	100	38
A 347	45	F	5 6 7	V_3	0	100	25	49
A 289	44	M	2	aV_R V_3 V_4 V_5 V_6	—	—	—	66
A 354	57	M	4	aV_R	0	50	0	78
A 360	47	M	1 3	V_1 V_3 V_4 Z	—	—	—	77
A 331	53	M	—	aV_R aV_L aV_F V_1 V_4 V_5 X	10	0	100	81
A 372	54	M	1	V_1	—	—	—	60
A 336	49	M	1 9	aV_R aV_L aV_F V_2 V_3 V_4 V_5m X,Y	75	0	0	100
A 387	55	M	0 5	X	100	0	100	68
A 390	47	M	1 4		25	75	100	61
A 95	47	M	1	aV_R aV_L	—	—	—	57
A 219	55	M	1	I II III V_1 V_4 V_6	—	—	—	90
A 377	65	M	6	I aV_R V_1 V_5 X	—	—	—	91

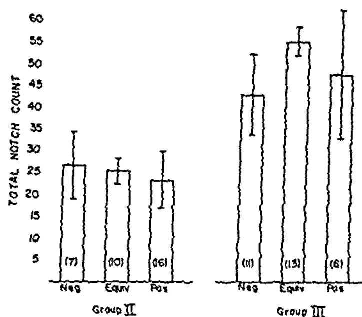


Fig 2 Comparison of the total notch count with the response to maximal treadmill exercise test in patients with angina pectoris (Group II) and MI (Group III)

In this group of patients (Group IIIa) we found a similar incidence of numbers of abnormally notched leads as in those patients with ECG s consistent with the clinical diagnosis of MI

The data presented in this report did not substantiate the previous observation[11] that high frequency components occur more often in patients with angina pectoris than in a normal group In that report it was shown that patients with a clinical diagnosis of ischemic heart disease and only nonspecific ST T changes had notch counts significantly higher than in the normal group Moreover, if the two step exercise test was positive in these patients a further increase in high frequency components was noted. However these authors also showed that notch counts were higher in some leads in patients with only angina pectoris than in the group with MI In our study the presence of a positive, equivocal, or negative maximal treadmill exercise test was not correlated with the significant differences in the notch count in either the angina group or the MI group Thus the high frequency ECG in our laboratory is not of prognostic value in delineating patients who may have a positive or negative maximal exercise test

Previous studies have not attempted to correlate coronary cineangiographic findings with the high frequency ECG In a study by Flowers and co workers [13] paraorthogonal Lead X was frequently found to be abnormal in the presence of anterior wall infarction, and Lead Y was often abnormal in inferior wall infarction We did find paraorthogonal Lead X and the lateral precordial leads to have the highest diagnostic specificity, but we were unable to correlate significant coronary artery obstruction with high frequency components in a given lead Our data suggest that given any abnormally notched lead or leads, it is not possible to predict the coronary vessel involved.

Although abnormal Q waves frequently failed to correlate with high frequency components, abnormal high frequency components were often present in the QRS complexes of leads adjacent to those showing abnormal Q waves It is sug

gested that a transmural infarction may show no abnormal high frequency components because such tissue is electrically silent On the other hand, tissue immediately adjacent to the infarction contains viable myocardium interspersed with fibrotic tissue [18] Such tissue may result in fragmentation of the propagating electromotive surface with the consequent development of high frequency components [6,8,12,19] Several of our observations support this hypothesis (1) patients with MI without persistent abnormal Q waves maintained a high total notch count (2) the high frequency ECG may show abnormally notched leads other than those demonstrating an abnormal Q wave (Table VII and Fig 1) (3) precordial leads immediately adjacent to an infarction often demonstrate high frequency components (not shown)

The above discussion supports the tenet that anatomic disruption of the myocardium is necessary for the development of high frequency components Yet, it is reasonable to ask are anatomic changes required to induce high frequency components ?* Our data from the anginal group suggests that in the resting pain free steady state high frequency components do not develop However we do not know whether such alterations might not occur during the anginal attack It has been shown[20] that transfiber conduction (i e conduction perpendicular to the longitudinal axis) is associated with slow conduction and a fragmented electromotive surface providing a physiologic basis for high frequency components However it has not been shown that ischemia per se will induce transfiber conduction Our observation that the anginal group failed to develop high frequency components *suggests* that anatomic changes are minimal or have not occurred.

Evidence accumulated from hypertrophied hearts[13,14,21] also supports the tenet that competing electromotive surfaces may result in distortion of the normally smooth contour of the QRS complex The genesis of the notch must necessarily be multifactorial[13] and hence compromise the diagnostic specificity of the high frequency ECG

*Ten patients were observed during maximal treadmill exercise testing and, despite the development of ST T wave changes, no change in the high frequency ECG was observed. However only one lead was recorded and changes may have occurred had multiple leads been utilized.

Summary

The high frequency ECG clearly contains information not available in the conventional ECG Patients with angina pectoris could not be identified as statistically different from the normal group based on notching although isolated examples existed MI on the other hand manifested abnormal notch counts in the presence or absence of abnormal Q waves We were unable to correlate the treadmill exercise test or the site of the arterial lesion with the high frequency ECG Pathophysiologic mechanisms are discussed

The authors are indebted to Dr Paul L. McHenry for providing data from the exercise laboratory Dr John F Phillips for providing coronary cineangiographic data and Drs Suzanne B Knoebel and Charles Fisch for their valuable advice in conducting this research

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Table VII Clinical, coronary cineangiographic, and abnormal lead data obtained from Group IIIa

Study No	Age	Sex	Age MI (years)	Abnormal leads	Cine			Total notches
					RCA	LAD	LCA	
A 367	49	M	1	aV_R	0	50	100	38
A 347	45	F	5 67	V_3	0	100	25	49
A 289	44	M	2	aV_R V_3 V_4 V_5 V_6	—	—	—	66
A 354	57	M	4	aV_R	0	50	0	78
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A 336	49	M	1 9	aV_R aV_L aV_F, V_2 V_3 V_4 V_5m X,Y	75	0	0	100
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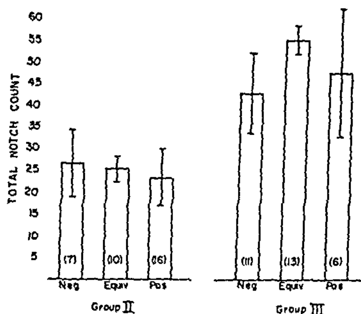


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Case reports

Bacterial endocarditis in idiopathic hypertrophic subaortic stenosis

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Bacterial endocarditis has been recognized as a complication of idiopathic hypertrophic subaortic stenosis (IHSS) A number of such cases[1-7] have been reported in the English literature but in only a few of these cases has the heart been examined either at operation or at necropsy Pathologic findings have demonstrated that bacterial endocarditis in IHSS may involve the aortic valve the mitral valve or both

The clinical course of bacterial endocarditis may be acute or chronic When the course is acute cardiac failure and sepsis predominate when the course is chronic immunologic manifestations such as nephropathy anemia and vasculitis predominate[8] The indolent course of bacterial endocarditis in a patient with IHSS and the findings at necropsy prompted us to record this case

Case report

A 43 year-old white man, plumber was admitted to the hospital because of generalized edema malaise and brown urine The patient had been well until four months *prior to* admission when he noted the onset of intermittent ankle swelling and dark urine During the two weeks *prior to* admission edema had become extensive resulting in a 32 pound weight gain During the same period he also experienced chills, drenching night sweats and malaise The patient denied shortness of breath orthopnea syncope paroxysmal nocturnal dyspnea or chest pain He had been taking no medication

Four years previously the patient was first informed that he had a h art murmur but was asymptomatic and no further diagnostic tests were performed Intermittent hypertension had been noted but not treated during his military service at 22 to 24 years of age There was no family history of heart disease

On admission to the hospital the patient was alert and oriented but appeared chronically ill Edema involved the eyelids hands abdomen scrotum penis and legs The supine blood pressure was 150/90 mm Hg The pulse rate was 110 beats per minute the temperature was 100 6 F There were bilateral conjunctival hemorrhages The ocular fundi were normal Many carious teeth were present The arterial pulse rose abruptly but was not bisferiens in character The neck veins were distended to the angle of the jaw when the trunk was elevated at 45 degrees and a prominent jugular venous A wave was present Moist râles were present in both lung bases The precordium was active with a palpable apical presystolic wave A harsh systolic ejection murmur was h ard at the apex and the left sternal border but no diastolic murmur was noted An atrial gallop (S_4) and a soft early diastolic gallop (S_3) were present The liver was enlarged and its lower border was 8 cm below the right costal margin. The spleen was enlarged with its lower border 9 cm below the left costal margin Petechiae showered the lower extremities Mild clubbing of the fingers was present There was no splinter hemorrhage or Osler s node The neurological examination was normal

Laboratory findings were a hemoglobin of 9 6 Gm per 100 ml a white blood count of 9 500 per cubic millimeter The urine contained packed red blood cells and 10 to 20 white blood cells per high power field and 3 4 Gm of protein in a 24 hour specimen The blood urea nitrogen was 36 mg per 100 ml the creatinine was 2 2 mg per 100 ml with a creatinine clearan e of 5(c c per minute The serum albumin was 2 8 Gm per 100 ml and the total protein was 6 0 Gm per 100 ml The serum Na was 120 mEq per liter K 5 2 mEq per liter Cl 99 mEq per liter and bicarbonate 18 2 mEq per liter The cholesterol was 142 mg per 100 ml The serum gamma globulins were elevated to 28 8 per cent of the total serum protein A direct and indirect Coombs te t and a lupus erythematosus cell clot test were negative

The chest roentgenogram revealed generalized cardiomegaly prominence of the ascending aorta increased vascular markings in the upper lung fields and bilateral small pleural effusions more marked on the right side than the left (Fig 1) No calcification was noted within the cardiac shadow Sinus tachycard a 100 per minute and a PR inter

From the Veterans Adm nistration Hospital and the D partme ts of Medicine a d P thology U i rs ty f M n sota School of M d c n M n polis Mi n

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Fig 1 Chest roentgenogram in posteroanterior *(A)* and lateral projections *(B)* reveal generalized cardiomegaly and bilateral pleural effusions

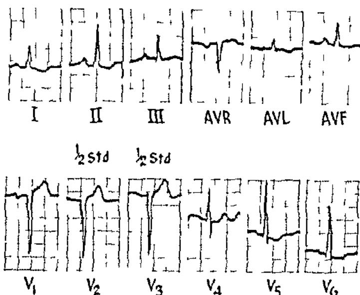


Fig 2 *The ECG reveals a PR interval of 0 20 sec deep QS waves in the anterior precordial leads and ST T changes in* the inferior and anterolateral leads consistent with left ventricular hypertrophy (Leads V_2 and V_3 are standardized at 1 mv = 5 mm)

val of 0 20 second was recorded on the ECG (Fig 2) There was poor progression of the R waves with deep QS waves in the anterior precordial leads and ST T changes in the inferior and anterolateral leads consistent with left ventricular hypertrophy An atrial gallop and systolic ejection murmur were recorded on a phonocardiogram (Fig 3) The carotid pulse revealed a rapid upstroke followed by a double wave form suggestive of IHSS[1] A prominent A wave was recorded in the apexcardiogram

All eight blood cultures drawn were positive for an enterococcus which was sensitive to penicillin lincomycin and sodium cephalothin The urine culture was also positive with more than 100 000 colonies of enterococcus per milliliter

The patient was treated with intravenous penicillin G 21 000 000 units per day digitalis and diuretics During the first week of treatment the edema decreased, 12 pounds were lost and the temperature decreased from 102 to 99 F On the tenth hospital day the patient developed a generalized erythematous papular dermatitis thought to be due to penicillin allergy Intravenous lincomycin 2 Gm every eight hours, was substituted for penicillin. On the seventeenth hospital day a murmur of aortic insufficiency was first heard. The temperature remained elevated at 100 F On the eighteenth hospital day aided by the drug sensitivity studies lincomycin was replaced by sodium cephalothin 16 Gm per day and streptomycin 1 Gm every other day With this regimen the temperature became normal and remained so except for an occasional rise to 100 F The patient s general condition improved

On the twenty sixth hospital day the patient became confused and agitated, and was treated with chloropromazine Gross hematuria continued and the blood urea nitrogen increased from 36 to 100 mg per 100 ml while the serum creatinine increased to 8 mg per 100 ml Hydrocortisone 150 mg daily was started During the ensuing four weeks the cardiac and renal status improved and hydrocortisone was discontinued on the fifty sixth hospital day The blood urea nitrogen and the serum creatinine decreased to 13 and 1 1 mg per 100 ml respectively The patient s mental status continued to deteriorate however and on the sixty fourth hospital day he had a grand mal seizure and developed left hemiparesis Confusion worsened A brain scan revealed a large area of increased radioactivity in the right parietal area The patient died on the sixty seventh hospital day

Pathologic features

At necropsy ventricular hypertrophy of the IHSS type bacterial endocarditis of the mitral and aortic valves glomerulonephritis and a massive intracerebral hematoma were the major findings

The heart was markedly hypertrophied and weighed 610 grams The left ventricular free wall was 2 cm thick (Fig 4) The ventricular septal

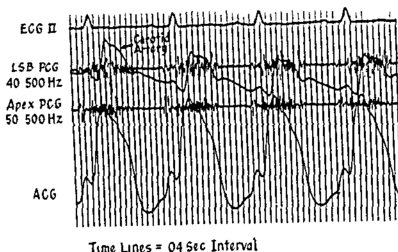


Fig 3 A phonocardiogram with microphones at the left lower sternal border and the cardiac apex simultaneously demonstrate a systolic ejection murmur and an atrial gallop sound Prominent "A" waves are visible in the apexcardiogram *(ACG)* The carotid arterial pulse tracing reveals a rapid upstroke with a double wave form suggestive of IHSS Pulse tracings were obtained from an Electronics for Medicine Inc PS 2 ceramic microphone with a time constant of 1 2 sec in the pulse position

musculature was quite prominent and measured 2 5 cm in thickness The septal prominence of the left ventricular outflow tract was highlighted by a thick fibrous plaque characteristic of IHSS [9] This suggested repeated trauma of long duration from the abutment of the anterior mitral leaflet to the ventricular septum The anterior mitral leaflet was also thickened. There were irregular firm vegetations in the center of the anterior mitral leaflet on both the ventricular and the atrial aspects The infectious process extended to the chordae tendineae and many of them mainly those from the posteromedial papillary muscle to the anterior mitral leaflet were ruptured with bulbus formation of the torn ends Vegetations were also present in the center of the atrial aspect of the posterior mitral leaflet where it came in contact with the lesion of the anterior mitral leaflet There was neither commissural fusion nor calcification of the mitral valve Vegetations were present on the ventricular aspect of all three aortic cusps but were more prominent on the posterior and the right aortic cusps (Fig 5) These vegetative lesions were limited to the coapting surface of the three aortic cusps Microscopic sections of these vegetative lesions revealed organizing granulation tissue without organisms The remainder of the aortic valve was normal The aorta above the aortic valve was also normal The left atrial endocardium was thickened but was not involved in the infectious process

The right ventricle was moderately hypertrophied and was 8 mm thick in its free wall There was an anomalous muscle bundle attached from the septal wall to the anterior wall of the right ventricle This muscle bundle divided the right ventricle into two channels both leading to the right ventricular infundibulum

The coronary arteries were devoid of any significant lesions and were widely patent

Examination of the brain revealed a massive right cerebral hematoma with herniation and necrosis of the right parahippocampal gyrus (Fig 6) This hematoma resulted from rupture of the right middle cerebral artery presumably from a mycotic aneurysm

Examination of the kidneys revealed cortical infarcts chronic passive congestion and crescent lesions of glomerulonephritis Chronic passive congestion of the lungs liver and spleen and hemorrhagic infarcts of the spleen were also present

Discussion

The clinical findings suggestive of IHSS in this patient were supported by three anatomic criteria of this disorder (1) dysproportionate hypertrophy of the interventricular septum (2) an endocardial fibrous plaque in the left ventricular outflow tract and (3) thickening of the anterior mitral leaflet [9]

The incidence of bacterial endocarditis in patients with IHSS varies from five to nine per cent



Fig 4 The left ventricle (*LV*) is opened to expose the endocardial surface mitral valve papillary muscles and the left ventricular wall thickness *The left ventricle is markedly hypertrophied, especially the interventricular* septum The septal prominence in the left ventricular outflow tract is lined by thick fibrous plaque characteristic of IHSS (black arrow) Many chordae tendineae from the posteromedial papillary muscle (*PM*) to the anterior *mitral leaflet* are ruptured with bulbus formation of the torn ends (white arrows) The anterior mitral leaflet (cut through the center) is thickened and is covered with vegetation The left atrial endocardium is thickened but devoid of any infectious process (*AV* = aortic valve)

in reported series[5,6,10] Among 126 patients with IHSS reported by Frank and Braunwald[5] three had documented bacterial endocarditis and an additional three patients had suspected bacterial endocarditis Swan and associates[10] noted four cases of bacterial endocarditis in a series of 85 patients with IHSS The two cases of bacterial endocarditis reported by Epstein and Coulshed[6] were from a total of 22 patients with IHSS The patient reported here is the second case of bacte rial endocarditis among 26 cases of IHSS ob served by us during the past four years

Including the case reported here the English literature contains anatomic observations in seven cases of bacterial endocarditis complicat ing IHSS[1-7] Observations include those made at necropsy (four cases) and at operation (three cases) The infection involved only the aortic valve in two patients[3,5] only the mitral valve in one patient,[4] both the aortic and the mitral valve in two patients[1] In the remaining two patients no pathologic evidence for previous bacterial en docarditis could be found even though the clini cal manifestations were convincing for bacterial endocarditis Rupture of the mitral chordae ten dineae noted in our case has not been reported previously

Necropsy findings in our case suggest that the infectious process originated in the center of the ventricular aspect of the anterior mitral leaflet This area is commonly thickened in IHSS due to trauma from the abutting action of the anterior mitral leaflet against the prominent ventricular septum[9] The infectious process may have then extended through the full thickness of the an terior mitral leaflet causing a contact lesion on the atrial aspect of the posterior mitral leaflet The infection also extended to the chordae ten dineae, resulting in rupture of several chordae Although bacterial endocarditis may have devel oped on a previously normal aortic valve it is more likely that the infection developed on pre viously damaged endothelium The verrucal le sion developed on the coapting surfaces of the aortic cusps in this case A midsystolic jet of blood passing through the AV at high velocity may have created a Venturi effect and caused the leaflets to vibrate against one another Over a



Fig 5 Aortic valve opened to expose the ventricular surface of all three aortic cusps Vegetative lesions are evident on the coapting surface (arrows) There is no commissural fusion or valvular calcification.

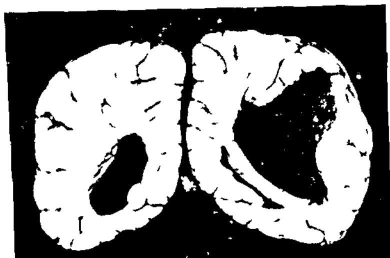


Fig 6 Coronal section of the brain through the cerebral hemispheres reveals a massive hematoma of the right cerebral hemisphere compressing the lateral ventricle

number of years the endothelium could have thus been damaged and served as a seat for bacterial endocarditis[11]

In an attempt to better understand the pathogenesis of bacterial endocarditis in patients with IHSS we have compared the pathologic findings with those of patients who had discrete membranous subaortic stenosis and bacterial endocarditis (Table I) In 10 reported cases of bacterial endocarditis in patients with discrete membranous subaortic stenosis the infection involved the aortic valve in all the aorta above the aortic valve in six the mitral valve in four and the membranous ridge in three[12-19] The high incidence of involvement of the aortic valve and aortic wall in this condition when compared to bacterial endocarditis in IHSS suggests that there is a more prominent jet in discrete membranous subaortic stenosis and that this jet causes more damage to the aortic leaflets and to

Table I Site of bacterial infection

Underlying disease	No of patients	Site of bacterial infection				
		Valve			Aortic wall	Membranous ridge
		Aortic only	Aortic and mitral	Mitral only		
1 IHSS	5	2	2	1	0	–
2 Discrete membranous subaortic stenosis	10	6	4	0	6	3

the aortic wall than occurs in IHSS Indeed when aortic flow is measured in patients with IHSS much of the stroke volume is ejected during the early part of the systole when there is no obstruction to left ventricular outflow and the remainder occurs later in systole when there is outflow obstruction [20] Discrete membranous subaortic stenosis is similar to valvular aortic stenosis in that there is obstruction to the left ventricular stroke volume during all of systole Aortic insufficiency is also much more common in discrete membranous subaortic stenosis with bacterial endocarditis (eight out of 10 patients) than in IHSS with bacterial endocarditis (five out of 18 patients) [1,7] Infection of the ascending aorta has not been reported in IHSS with bacterial endocarditis whereas it is common in patients who have the discrete membranous type (six out of 10 patients) In four of these six patients with infection involving the aortic wall a mycotic aneurysm was present One patient died from the rupture of this aneurysm Infection involves the mitral valve in about the same frequency in both discrete membranous and in muscular subaortic stenosis but the pathogenesis is apparently different In discrete membranous subaortic stenosis, the mitral valve becomes infected either as a part of the infection on the membranous ridge which is attached to the anterior mitral leaflet or as a satellite lesion from aortic regurgitation associated with an infected aortic valve [21] In IHSS the mitral valve becomes more susceptible to infection presumably due to the repeated trauma on the anterior mitral leaflet by its abutting action against the septal prominence [9]

The prognosis of patients with bacterial endocarditis complicating IHSS is not different from that of bacterial endocarditis in general Of the 18 patients reported in the English literature with bacterial endocarditis complicating IHSS (including two in our series) four patients died in the hospital a hospital mortality rate of 22 per cent which is comparable to the hospital mortality rate of 30 per cent for bacterial endocarditis in general [22] In addition the bacteriology, precipitating factors and systemic manifestation do not appear to be unusual in patients with bacterial endocarditis complicating IHSS The mortality rate in bacterial endocarditis is more reasonably related to the sensitivity to antibiotics of the invading organism and to the duration between the onset of bacterial endocarditis and to the onset of treatment. In the patient reported a long interval of time elapsed from the onset of infection to the onset of treatment In such patients the mortality rate is high and patients are more likely to die of immunologic complications of bacterial endocarditis in spite of a bacteriologic cure' The nephropathy, dysproteinemia anemia and vasculitis were more prominent problems in our patient than were problems due to infection or cardiac failure The cerebral hemorrhage which proved fatal is common in patients with bacterial endocarditis who have a long indolent course before the institution of appropriate antibiotic therapy [8] In a series of 19 cases of enterococcal endocarditis the mortality rate was 70 per cent (five deaths in seven patients) in patients whose illness was present more than three months before definitive therapy, whereas in patients who received definitive therapy within three months or less the mortality rate was 33 per cent (four deaths in 12 pa

tients)[23] Nephropathy became severe and was the most prominent feature in our case until intracerebral bleeding led to death of the patient

Aortic insufficiency developed during endocarditis in this patient This sequence of events has been observed in three other reported cases[3 5 6] Aortic insufficiency occasionally associated with IHSS may represent healed bacterial endocarditis of the aortic valve

Summary

Bacterial endocarditis complicating idiopathic hypertrophic subaortic stenosis (IHSS) is uncommon but endocarditis may be the first clinical manifestation of IHSS In this report of such a case the aortic and the mitral valves were the sites of the bacterial infection Many chordae tendineae to the mitral valve were ruptured from the extension of the infectious process The endothelial lesions which served as the seat for the bacterial infection on the anterior mitral leaflet likely resulted from its abutting action against the septal prominence Damage to the aortic valve leaflet may have resulted from abnormal valve motion caused by IHSS and created an environment conducive to endocarditis This patient developed aortic insufficiency during the course of bacterial endocarditis suggesting that the occasional association of aortic insufficiency in patients with IHSS may be secondary to healed endocarditis of the aortic valve

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Aneurysm formation A late complication of venous by-pass grafting

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Progression of arteriosclerosis is a complex process dependent not only on factors within the arterial wall but also on hydrostatic pressure The importance of systemic blood pressure is illustrated by development of atherosclerosis in autogenous venous grafts used to replace arterial segments[1] The patient reported below suffered an unusual sequela of this process—aneurysm formation

Case report

A 74 year-old woman was hospitalized with a three week history of an enlarging pulsatile mass in her right thigh Six years previously successful right femoropopliteal bypass surgery with an autogenous saphenous vein had been performed because of intermittent claudication For the past two years she had noted two block claudication in the left calf She had no history of cardiopulmonary disease or diabetes mellitus.

Examination revealed a slightly obese woman with a blood pressure of 150/90 mm Hg and pulse rate of 65 per minute Pertinent physical findings were confined to the lower extremities A nontender pulsatile mass about 3 cm in diameter was palpable in the right medial thigh 12 cm below the inguinal ligament Strong femoral pulses and a weak right popliteal pulse were present but the left popliteal and all tibial pulses were missing The feet appeared healthy with no evidence of blanching on elevation or dependent rubor

Laboratory work Hemoglobin 12 8 Gm per 100 ml white blood count 9 800 per cubic millimeter urinalysis, normal blood urea nitrogen 16 mg per 100 ml fasting blood sugar 72 mg per 100 ml cholesterol 298 mg per 100 ml chest x ray and electrocardiogram normal Aortography via the left femoral artery revealed mild dilatation of the terminal aorta (3 cm in diameter) and a large saccular aneurysm of the saphenous vein graft in the right upper thigh (Fig 1) The graft was also very tortuous and irregular with multiple areas of stenosis The left superficial femoral artery was totally obstructed

Hospital course Because of the danger of rupture of the enlarging aneurysm surgical repair was undertaken The graft was calcified and cord like but patent and a short Dacron graft was interposed between the cut ends of the saphenous vein The postoperative course was uneventful and the patient was discharged to clinic

Pathology The surgical specimen consisted of a markedly dilated segment of vein measuring 5 cm in maximal width (Fig 2) It was heart shaped and the apex was extremely thin There was a large laminated thrombus within the aneurysmal sac (Fig 3) Microscopic sections revealed arteriolization and atheromatosis of the vein The lumen was attenuated by atheromatous deposits in the intima and marked intramuscular and adventitial fibrosis was present An elastic stain showed disruption of the elastica (Fig 4)

Discussion

Histologic study of vein grafts from amputated limbs has shown that a vein anastamosed at each end to an artery tends to become an arterial structure[1] with elastic tissue taking on an arterial pattern This relatively thin arterialized vein is subject to progressive occlusive atherosclerosis and it is reasonable to presume that progressive aneurysmal dilatation might occur eventually in susceptible patients However, in long term follow up studies this complication

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Fig 1 Arteriogram demonstrating an aneurysm in the saphenous vein graft. The obstructed superficial femoral artery is shown running parallel to the venous graft

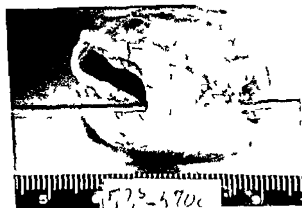


Fig 2 Aneurysm as it appeared at surgery



Fig 3 Aneurysmal sac with laminated thrombus

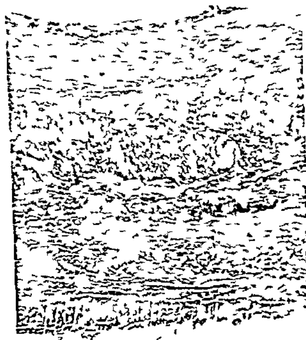


Fig 4 Microscopic section of venous graft showing subintimal thickening (upper layer) muscular hypertrophy (middle layer) and splintered elastic fibers (black lines) (Elastic stain ×20 ×5)

has not been reported.[2,5] Our patient is only the third to be reported with an arteriosclerotic aneurysm of an autogenous vein graft in the femoropopliteal region As in the previous two cases [6,7] the aneurysm did not appear until several years after surgery Perhaps extensive atherosclerosis in the vein graft leads to occlusion before aneurysms can develop This would be consistent with the behavior of the superficial femoral artery which frequently occludes but rarely becomes aneurysmal

Risk of aneurysm formation assumes even greater clinical significance when saphenous veins are used for arterial grafting in areas where they cannot be examined directly Ernst and associates [8] in reviewing results of surgery for renal artery stenosis found vein graft aneurysms in 5 of 53 (9 per cent) patients undergoing renal arteriography after a mean postoperative period of 37 months The development of coronary artery surgery has led to a marked increase in the use of saphenous vein

grafts Although aneurysmal dilatation is apparently unusual when the vein is closely surrounded by relatively firm thigh muscles, this lesion may be a more common late complication when the vein is stretched across the epicardial surface from aorta to coronary artery The consequence of an aneurysm in the coronary bed could be either rupture or recurrent myocardial infarction secondary to mural thromboembolism Long term follow up of patients after coronary artery surgery with serial coronary arteriography will be necessary to assess the magnitude of this risk

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Review

Primary chylopericardium a review of the literature and an illustrated case

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The normal adult pericardial cavity contains approximately 25 to 35 c c of serous fluid which is essentially identical to lymph [1] Increase in the amount of this fluid may occur secondary to various disease states such as pericarditis generalized edema and cardiac failure In addition under certain pathologic conditions the composition of this fluid may be altered to one of a serosanguineous cholesterol or chylous nature The purpose of this paper is to report a case of chylous pericardium and to review previously reported cases of this entity

Review of the literature

Isolated chylopericardium was first reported in 1888 by Hasebrock[2] who described 22 6 c c of chylous fluid removed at autopsy from a patient who died of aspiration secondary to tracheal stricture and ulceration In reviewing 100 cases of nontraumatic chylothorax in 1935 Yater[3] noted three cases of associated chylopericardium In 1954 the clinical entity of primary chylopericardium was first recognized by Groves and Effler[4] who used the term to describe isolated accumulation of chyle in the pericardium with no known etiologic mechanism There have since been twenty additional cases of this entity reported in the world literature [5-24] Data compiled from these case reports are presented in Tables I II and III

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Case report

Present illness The patient was an 11 year-old boy who was referred to the clinic for evaluation of an enlarged cardiomediastinal silhouette (Fig 1) noted on plain chest film taken one week earlier to follow a left lower lobe pneumonia Review of a chest film taken at 2 5 years of age also revealed an enlarged cardiomediastinal silhouette (Fig 2) The patient had experienced bouts of left lower lobe pneumonia at 2 5 9 and 11 years of age There was a recent increase in fatigability with exercise Two months earlier he had been hospitalized overnight following a cerebral concussion (momentary loss of consciousness, headache and dizziness) from a head injury while playing football

Physical examination. The physical examination showed a well developed male with a regular pulse of 98 per minute and a blood pressure of 100/75 mm Hg The neck veins were normal. The chest was clear to auscultation On auscultation of the heart there was no murmur or click. The point of maximum impulse was diffuse and the heart sounds were distant The remainder of the physical examination was within normal limits

Laboratory data. Plain chest x rays showed an enlarged cardiomediastinal silhouette Echography demonstrated a large fluid filling pericardial space Electrocardiogram recorded a non specific ST segment elevation in Leads V_5 and V_6 and a shortened PR interval. Skin tests were normal. Blood counts were as follows hemoglobin, 14 1 Gms per cent hematocrit, 40 5 per cent and white blood cell count 5 000 per cubic millimeter with 59 per cent neutrophils 20 lymphocytes 8 monocytes and 11 eosinophils

Hospital course The patient was hospitalized after being followed for six months during which he had experienced several occasions of extreme fatigue after exercise with syncopal episodes and slight cyanosis Right heart catheterization showed normal right atrial and pulmonary vein wedge pressures. Pericardiocentesis obtained 630 c c of milky fluid Introduction of air at this time confirmed the gross pericardial effusion (Fig 3) The diagnosis of chylopericardium was made from the milky appearance and the lipoelectrophoretic pattern of the aspirate which was characteristic of chylomicrons Lymphangiogram showed no contrast accumulation in the pericardium

The patient was discharged and readmitted in three weeks with reaccumulation of the pericardial fluid. A right thoracotomy was then performed during which a multiple channeled thoracic duct network was noted No tumor or abnor

Table I Summary of symptoms, physical findings, and treatment in reported cases of chylopericardium

Reference	Age	Sex	Presenting symptoms	Presenting physical findings
1 Grooves and Effler (1954)	31 yrs.	F	Dizzy spells dyspnea ×9 months	Distended neck veins enlarged heart by percussion
2 Naef (1956)	14 mos	F	Cough dyspnea acute onset	–
3 Madison and Louge (1957)	40 yrs	F	Exertional and nocturnal dyspnea dependent edema × 7 years	Enlarged heart by percussion
4 Stratton and Grant (1958)	1 day	F	Respiratory distress at birth	Cervical and axillary subcutaneous cystic masses
5 Miller et al (1959)	15 yrs	F	Dyspnea orthopnea × 1 month	Tachypnea paradoxical pulse peripheral cyanosis distended neck veins enlarged heart by percussion enlarged liver
6 Bartel and Nettler (1964)	6 yrs	M	Asymptomatic	Distant heart sounds
7 Knight (1965)	62 yrs	M	Dyspnea fatigability cough × 6 months	Distended neck veins enlarged heart by percussion distant heart sounds
8 Hudspeth and Miller (1966)	22 yrs	M	Asymptomatic	Enlarged heart by percussion
9 Yankopoulos et al (1967)	40 yrs	M	Asymptomatic	Enlarged heart by percussion apical protodiastolic gallop after exertion
10 Fawal et al (1967)	36 yrs	M	Epigastric and substernal fullness and discomfort × 2 years	Enlarged heart by percussion distant heart sounds
11 Glasser et al (1968)	23 yrs	F	Asymptomatic	Normal
12 Goldstein (1969)	21 yrs	F	Asymptomatic	Normal
13 Daniel and Bressie (1969)	38 yrs	M	Feverish cough compressive substernal pain dyspnea orthopnea fatigability > 6 months	Enlarged heart by percussion distant heart sounds atrial gallop enlarged liver
14 Yoshida et al (1969)	10 yrs	M	Fatigability dyspnea cough hemoptysis > 2 months	Paradoxical pulse distended neck veins enlarged heart by percussion distant heart sounds enlarged liver
15 Rouchu and Jouve (1969)	32 yrs	F	Palpitation fullness in left subclavicular area	Distant heart sounds
16 Modai et al (1970)	19 yrs	M	Asymptomatic	Distant heart sounds
17 Thomas and McGoon (1971)	31 yrs	F	Increasing fatigue > 1 month	Venous distention
18 Hawker et al (1972)	9 wks	F	Restlessness respiratory distress rapid onset	Cyanosis hepatomegaly poor peripheral circulation
19 Puig Massana (1972)	12 yrs	M	Asymptomatic	Systolic click at left sternal border
20 Csanady and Kovacs (1973)	26 yrs	F	Dyspnea nocturnal ankle edema > 6 years	Distant heart sounds
21 Chavez et al (1973)	27 yrs	M	Asymptomatic	Slightly distant heart sounds
22 Present case	12 yrs	M	Increasing fatigue	Distant heart sounds

Operative findings/etiology	Treatment	Results
Mediastinal hygroma	Left thoracotomy—pericardial window: right thoracotomy—ligation t duct pericardial window	6 months—no reaccumulation
Unknown ? injury	Right thoracotomy—ligation t duct surrounding tissue and azygous vein	2 years—no reaccumulation
Unknown	Right thoracotomy—ligation t duct and collaterals pericardial window	1 year—no reaccumulation
Multicystic mediastinal hygromas	Sternotomy—excision of masses pericardial window	3 months—reaccumulation and death
Hamartomatous lymphangiomatosis with lymphangiectasis of lungs pleura and pericardium	Left thoracotomy—ligation lymphatics at base of pericardium pericardial window	47 days—reaccumulation and death
Unknown	Right thoracotomy—ligation t duct pericardial window	3 months—no reaccumulation
Unknown	Left thoracotomy—ligation t duct pericardial window	4 years—no reaccumulation
Unknown	Right thoracotomy—ligation, and resection (10 cm.) t duct pericardectomy	14 months—no reaccumulation
Unknown	Right thoracotomy—ligation and resection (4 cm.) t duct ligation surrounding tissue pericardial window	17 months—no reaccumulation
Unknown	Left thoracotomy—ligation lymphatic channels and t duct hemipericardectomy	7 months—no reaccumulation
Lymphangiectasis about left hilum shown with dye injection into t duct	Left thoracotomy—ligation t duct and tortuous lymphatics pericardial window	7 months—no reaccumulation
Superior mediastinal lymphangioma multiple lymphangioma of bone > 5 years	Left thoracotomy—ligation t duct and lymphatic channels excision of lymphangioma hemipericardectomy	2 months—no reaccumulation
Unknown	Right thoracotomy—ligation and resection long segment t duct ligation lymphatics pericardial window	6 months—no reaccumulation
Lymphangiectasis in superior mediastinum on lymphangiogram	No surgery (refused)	Reaccumulation after numerous pericardiocenteses
Unknown	Right thoracotomy—ligation and resection (10 cm.) t duct hemipericardectomy	7 months—no reaccumulation
Lymphangiogram—lymphatics right anterior mediastinum typical of lymphangioma	Left thoracotomy—pericardial window left thoractomy—ligation t duct and pericardial window	4 months—no reaccumulation
? Surgical sequelae thrombus left jugular subclavian venous confluence on venogram	Left thoracotomy—pericardial window: right thoractomy—ligation and resection segment of t duct	1 year—no reaccumulation
? Surgical sequelae	Pericardiocentesis medium chain triglyceride diet, × 4 weeks	8 months—no reaccumulation
Dye t duct—stained lymphatics at left hilus and accumulated in pericardium	Left thoracotomy—ligation and resection (2 cm.) t duct hemipericardectomy	9 months—no reaccumulation
Unknown	Sternotomy—hemipericardectomy	1 year—no reaccumulation
? Obstruction of t duct at midthorax on lymphangiogram	Subxyphoid—pericardial window with exterior drainage via tube	8 months—no reaccumulation
Unknown	Right thoracotomy—ligation and resection (5 cm.) t duct, pericardectomy	7 months—no reaccumulation

Table II Summary of findings of diagnostic procedures performed in reported cases of chylopericardium

Case	Plain Roentgenograms	Fluoroscopy	Angiography	Pericardial air	ECG
1	Cardiomegaly of ? duration	Absence of cardiac pulsations	—	—	Low voltage
2	Cardiomegaly of 1 month	—	—	—	Typical signs of pericarditis
3	Cardiomegaly > 7 years	Diminished cardiac pulsations	Suggested p eff	Confirmed p eff	Low voltage
4	Mediastinal widening at birth	—	—	—	—
5	Cardiomegaly > 2 years	Diminished cardiac pulsations	—	Confirmed p eff	ST depression low voltage low T in Leads II III AV_F
6	Cardiomegaly > 1 year	—	—	—	Normal
7	Cardiomegaly ? duration	—	—	—	Low voltage flattened T in Leads I and AV_L
8	Cardiomegaly > 6 years	—	Suggested p eff	Confirmed p eff	Normal
9	Cardiomegaly > 6 years	Diminished cardiac pulsations	Suggested p eff	Confirmed p eff	Normal
10	Cardiomegaly > 1 year	Configuration of massive p eff*	—	—	Normal
11	Cardiomegaly > 2 months	—	Suggested p eff	Confirmed p eff	—
12	Cardiomegaly > 1 month	—	Suggested p eff	Confirmed p eff	Normal
13	Cardiomegaly > 2 years	—	Suggested p eff	—	T wave changes of digitalis effect
14	Cardiomegaly > 7 years	Configuration of p eff	Suggested p eff	—	Low voltage
15	—	Cardiomegaly diminished pulsations	Suggested p eff	—	Low voltage QRS
16	Cardiomegaly	Diminished cardiac pulsations	—	—	Low voltage Leads I and AV_L
17	Cardiomegaly < 2 months	—	Left jugular subclavian thrombus	—	—
18	Cardiomegaly > 5 weeks	Diminished cardiac pulsations	—	—	—
19	Cardiomegaly	—	Suggested p eff	—	Low voltage
20	Cardiomegaly > 15 years	—	Suggested p eff	—	Low voltage
21	Cardiomegaly > 6 months	—	Suggested p eff	—	—
22	Cardiomegaly > 8 years	Diminished cardiac pulsations	Suggested p eff	Confirmed p eff	ST elevation Leads V_5 V_6 shortened PR interval

p eff = pericardial effusion

†p asp = pericardial aspirate

mal dilation of lymphatics was seen The thoracic duct above the diaphragm was ligated and a segment was resected A pericardectomy was performed and the operative recovery was uneventful The cardiomediastinal silhouette became normal and remained normal at ten months postoperatively (Fig 4)

Discussion

Chylous pericardium has been documented from the newborn period to forty years of age It occurs with equal frequency in males and fe males The presenting condition of the patient

Lymphangiogram	Sudan II PO
–	Stained p asp†
–	–
–	Stained p asp
–	–
–	Stained p asp
–	–
–	–
Normal	Stained p asp
Normal	–
–	–
–	–
Puddling of contrast in pericardium on 24 hour films	–
–	–
Lymphangiectasis in superior mediastinum contrast in pericardium on 6 day films	–
Normal	–
Lymphatics right anterior mediastinum typical of lymphangioma	–
–	–
–	–
Normal	–
–	–
? Obstruction with proliferation of lymphatic mid thorax two week postoperative pooling in area of left main stem bronchus	–
Normal	–

may vary from asymptomatic (8 out of 22 cases) to one of severe respiratory difficulty and cardiac tamponade (1 out of 22 cases) Physical signs appearing with chylous pericardial effusion have included diminished heart sounds (10 out of 22 cases) enlarged heart silhouette by percussion (9 out of 22 cases) distended neck veins (5 out of 22 cases) enlarged liver (3 out of 22 cases) and pulsus paradoxus (2 out of 22 cases)

Diagnosis The specific diagnosis of chylous pericardium can be made with pericardiocentesis and analysis of the aspirate It is important that the constituency of the fluid in a pericardial accumulation be determined early for the proper and successful management of these patients depends on the confirmation of the chylous nature of the fluid Several (7 out of 22 cases) of the reported cases were treated for tuberculous pericarditis before the correct diagnosis was made[4,6,8,13,17,19]

Chylous fluid is characterized by two main features—its milky white appearance and the presence of fat droplets microscopically The chemical makeup of the fluid is variable since the composition depends on the diet[5] Its cholesterol content has ranged from 67 mg per cent to 177 mg per cent Protein content ranges from 3 15 gm. per cent to 7 6 gm per cent Cytologic analysis has revealed white blood cell counts of few to 7 300 per cubic millimeter and, with the exception of a single case these have been lymphocytes When culture has been performed, all cases have been negative a finding compatible with the reported bactericidal nature of the fluid[6]

Differentially cholesterol pericardium is the only other major consideration Its fluid has a golden hue and microscopically there are cholesterol crystals

Several techniques have been utilized in attempts to demonstrate a connection between the pericardial sac and the lymphatic system Groves and Effler[4] orally administered an oil stained with Sudan III followed by pericardial tap of the fluid and analysis for presence of stained fat droplets Similarly triolein tagged with I^{131} has been ingested with subsequent counts over the precordium and analysis of the pericardial aspirate[11] Both of these techniques have been employed successfully

Lymphangiography has been utilized in attempts to visually demonstrate communication of the thoracic duct with the pericardial sac In two instances[15,17] delayed films showed pooling of contrast in the pericardial sac Obstruction and anomalies of the thoracic duct have also been demonstrated with lymphangiography[17,19,24]

Other diagnostic procedures which have been



Fig 1 Chest roentgenogram at age eleven years showing enlarged cardiomediastinal silhouette and residual left lower lobe pneumonitis



Fig 2 Chest roentgenogram at age two and one half years showing enlarged cardiomediastinal silhouette and left lower lobe pneumonitis

utilized include fluoroscopy and angiocardiography The results of these and other procedures are shown in Table II

Etiology The exact etiology of chylous pericardium has not been shown The term chylous pericardium implies a communication between the pericardial sac and the thoracic duct carrying chyle Some investigators propose the existence of direct microscopic connections between the pericardial sac and the thoracic duct to account for chylous accumulation [9] However, no direct connection has been demonstrated Normal indirect communications do exist

The lymph vessels from the pericardium go to the anterior mediastinal, retrosternal diaphragmatic and bronchopulmonary lymph nodes and thence to the thoracic duct [25,26] Due to the presence of valves in lymphatic tributaries reflux cannot easily occur unless a thoracic duct pressure estimated to be approximately 15 cm of water, is exceeded [27] An increase in thoracic duct pressure as high as 35 to 50 mm Hg[28] can occur with partial or total obstruction of the duct thus allowing reflux along the normal channels In several animal studies,[29,30] obstruction of the lymphatics of the neck and mediastinum produced chylopericardium However, in other studies the thoracic duct was ligated cephalad to the heart and mediastinum without causing chylopericardium [31] Experiments have also shown that with ligation of the thoracic duct, lymphatic return may be established via the right thoracic duct or via collateral lymphaticovenous connections between the thoracic duct and the azygous vein[23,25] thereby relieving the pressure Thus, it would appear that lymphatic blockage alone would not necessarily result in reflux and chylous pericardium since other routes of drainage are possible

In Thomas [20] case, both surgical trauma to the normal lymphatic drainage of the pericardium and venous thrombosis in the jugular vein with possible subsequent blockage of the thoracic duct drainage into the left subclavian vein were felt to be contributing factors to the development of the chylous fluid In several of the cases herein reviewed [4,7,8,16,19] mechanical obstruction of the venous drainage and/or lymphatic drainage by tumor or hygromatous transformation of lymphatics were felt to have resulted in chylopericardium The notable point in these cases is the suggestion of obstruction of venous drainage in addition to lymphatic blockage, thus disallowing ancillary routes of lymphatic drainage Both types of obstruction with resultant chylothorax and chylopericardium have been produced in

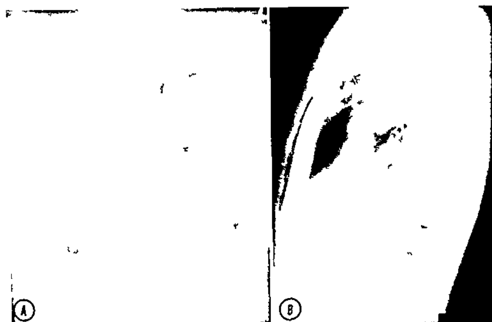


Fig 3 Chest roentgenogram following pericardiocentesis and introduction of air A normal sized heart is masked by a large chylous pericardial effusion

animals by ligation of the superior vena cava cephalad to the azygous vein [30] Chylothorax has also resulted from proposed lymphatic damage occurring during limited dissection posterior to the superior vena cava while obstructing it with tape in preparation for cardiopulmonary by pass [32,33]

It would appear that accumulation of chyle in the pericardial sac would depend on several fac tors (1) obstruction of the thoracic duct with resultant increase in pressure (2) failure to es tablish collateral lymph drainage to the right thoracic duct or lymphaticovenous connections to relieve the pressure and (3) reflux of chylous lymph through normal lymphatic channels or through channels lacking valves which drain the pericardium and heart.

Treatment Chylous pericardium has been suc cessfully treated by low thoracic duct ligation and establishment of a pericardial window (13 out of 22 cases) Others have been treated with partial pericardectomy alone (6 out of 22 cases) three of which required reoperation and thoracic duct ligation due to reaccumulation of the fluid and two of which died prior to reoperation One patient, who refused surgery was treated with pericardiocentesis only with reaccumulation of the fluid after numerous taps Another individual was treated with pericardiocentesis and medium



Fig 4 Chest roentgenogram ten months postoperative show ing no reaccumulation of pericardial fluid.

chain triglyceride diet with favorable results Es tablishment of a pericardial window with sub xiphoid exterior tube drainage was successful treatment in another case All patients who were eventually treated with thoracic duct ligation and pericardial window (16 out of 22 cases) had no reaccumulation of fluid.

Table III Summary of pericardial fluid analysis in reported cases of chylopericardium

Case	Appearance	Specific gravity	Cholesterol (mg %)	Triglycerides (mg %)	Protein (gm. %)	WBC (mm³)	Per cent PMN Lymphocytes	Culture	Other
1	Milky	1 018	133	—	3 15	600	0/100	Negative	Sudan III
2	Milky	—	118	—	4 2	—	—	Negative	Lipids 0 8 Gm %
3	Milky	1 014	140	—	5 4	2 750	0/100	Negative	Fat 0 6 Gm %
4	Thin white	—	144	—	—	—	—	—	Sudan III
5	Serosanguineous	1 025	103	573	4 9	—	—	Negative	Sudan III
6	Milky	—	—	—	—	Few	0/few	Negative	—
7	Milky	—	—	—	—	—	—	Negative	Fat droplets
8	Milky	—	—	—	—	—	—	—	Sudan III
9	Brownish yellow	—	125	1 051	—	4 400	0/90	Negative	Sudan III
10	Milky	1 036	140	1 640	5 9	280	0/100	Negative	Cleared with ether
11	Milky	1 045	172	—	7 2	4 000	0/100	Negative	Sudan III
12	Milky	—	105	1 000	5 5	7 300	0/100	Negative	Sudan III
13	Milky	1 022	137	—	5 3	—	—	—	Lipids, 0 6 Gm %
14	Chylosanguineous	—	137	—	6 4	—	—	Negative	Fat, 0 5 Gm*
15	Milky	—	140	40	3 5	—	—	Negative	Lipids, 1 3 Gm %
16	Milky orange	—	117	5 034	3 6	Few	0/100	Negative	Lipids, 5 4 Gm %
17	Milky	1 017	—	—	—	800	—	Negative	—
18	Chylous	—	—	—	—	—	—	Negative	—
19	Milky	1 020	170	—	6 8	1 400	0/100	Negative	Fat droplets
20	Milky	1 026	177	0	7 6	—	—	Negative	Lipids, 0 5 Gm %
21	Milky	—	—	—	—	—	—	—	—
22	Milky yellow	—	67	2 751	6 5	1 138	3/97	Negative	—

Summary

A report of a case of chylous pericardium and a review of previously reported cases are given The specific diagnosis can be made with pericardiocentesis and analysis of the fluid which is milky in appearance and contains fat droplets microscopically Thoracic duct obstruction with failure of adequate collateral drainage and resultant reflux of chylous lymph through lymphatics draining the heart and pericardium is proposed as a mechanism of development of this entity Thoracic duct ligation and partial pericardectomy remain the preferred treatment for chylopericardium

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The long Q-T syndrome

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The association of a prolonged Q T interval, congenital deafness and syncopal attacks due to ventricular fibrillation following emotional or physical stresses is a clinical entity known as 'Jervell and Lange Nielsen' syndrome[1] The absence of the congenital deafness characterizes the otherwise identical 'Romano Ward syndrome[2,3] Both conditions (long Q T syndrome) have a very high mortality rate and are recognized to contribute to sudden death in children[4]

The patients affected by the long Q T syndrome (LQTS) are characteristically likely to present episodes of alternation of the T wave following the same stimuli which trigger the syncopal attacks[5,6] and often these episodes of alternation precede or follow ventricular fibrillation

Since its first description in 1957,[1] progress has been made in the understanding and in the treatment of this often fatal syndrome In spite of these recent advances there is still much confusion about the LQTS and the uncertainty as to its pathogenesis often leads to the application of a variety of therapies and to the frequent change of drugs the general results being poor Moreover there are entirely too many patients who remain undiagnosed due to the lack of knowledge of this syndrome and eventually die

Nowadays the pathogenetic mechanisms although not completely elucidated, are better understood and effective treatments are available greatly reducing the risk of sudden death in patients properly treated

Case reports

In all the cases listed below the physical examination and laboratory investigations were negative and the syncopal attacks were provoked by violent emotions or physical exercise

Case 1 CB (this case was previously briefly mentioned[6]) was born on Aug 23 1951 This girl with normal hearing started having syncopal attacks when she was three years old. The frequency of the attacks was reduced with age from several per month to several per year When she was 18 years old she was admitted to a hospital after a syncopal attack that occurred while running after a bus She was found to be hyperthyroid and was subjected to a partial thyroidectomy No explanation was given for her syncopal episodes. The electrocardiogram (ECG) was considered normal but when we were able to obtain that tracing we found that the Q T interval was greatly prolonged (Q T_c 0 50) When she was 19 years old while part of a live audience in a television program she became quite emotional and suddenly died The necropsy was negative and her case remained undiagnosed Two brothers the mother and the maternal grandmother had a Q T interval slightly prolonged or at the upper limits of normal values (Q T_c from 0 43 to 0 46) two sisters are reported here as cases 2 and 3 This family originates from a small mountain village in Northern Italy It is noteworthy that the parents were second cousins

Case 2 AB (this case has been partially presented elsewhere[6]) was born on Aug 19 1961 Like the older sister this girl started having syncopal attacks when she was three years old and the attacks were fairly frequent (three to four times a week) She was referred to us in January 1971 and we observed that under the same conditions which provoked the syncopal attacks (emotions or exercise) she also presented some episodes of alternation of the T wave (Fig 1 A) After two exercise tests the Q T interval increased enormously while her heart rate was not modified (Fig 2) Since she was diagnosed as being affected by the LQTS (her Q T_c was 0 61) we started treating her with propranolol (up to 160 mg) Thereafter she had only 6 attacks per year showing that propranolol was effective in greatly reducing the frequency of syncopal attacks However since any of these episodes could prove fatal this therapy was not regarded as sufficient On the basis of the experimental results obtained by Yanowitz Preston Abildskov[7] and by ourselves[5,6] and of the successful surgical attempt reported by Moss and McDonald[8] a surgical treatment seemed rational In March 1973 AB was operated on the inferior part of the left stellate ganglion with the second and third thoracic ganglia were removed This type of sympathectomy does not produce a Horner syndrome For the sake of safety the medical treatment was not discontinued Immediately after the surgery the Q T interval became normal (Fig 2) for a couple of days but subsequently it started to increase progressively After

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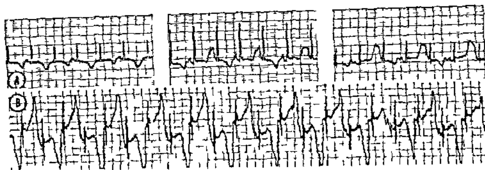


Fig 1 Episodes of alternation of the T wave in patients affected by the long Q T syndrome A Case 2 ECG (D1 D2 and D3) recorded during spontaneous fright B Case 5 Tracing obtained by monitor while the patient was in a coronary unit followed a few seconds later by ventricular fibrillation

one week it started to shorten again At six and seven months after the operation the Q T interval, though still prolonged had clearly moved toward the normal values (Q T 0 46) (Fig 2) The physical condition had dramatically improved the girl being able for the first time in her life to accomplish severe physical efforts. In the 18 months following the surgery she remained with one exception completely free from syncopal attacks The only syncopal episode occurred six months after surgery and was first thought to be a failure of the therapy However the patient told us that on the day of the attack she had failed to take propranolol and that in the preceding week she had been irregular in taking the drug It is important to note that in this extremely serious case neither therapy by itself was sufficient to eliminate the syncopal attacks while this result seems to be accomplished by the two therapies together However several years are necessary to draw any definite conclusion on this point. Her present values of propranolemia[9] are 340 ng per milliliter one hour after taking her regular dose (40 mg) and 150 ng per milliliter after four hours

Case 3 CB (the parents gave her the same name of the dead sister) was born on Nov 26 1972 This girl is now 19 months old. Although her Q T interval is extremely long (Q T 0 51) she has had no syncopal attacks However we are following her closely

Case 4 CC (case referred to us by Drs. Agostoni Folli and Rumolo Milan Italy) was born on Aug 31 1965 This boy started having syncopal attacks (three in two years) when he was six years old and in his first year at school His Q T interval is clearly prolonged (Q T_c 0 53) and he has an obvious bradycardia 56 beats per minute He has normal hearing The ECG of the father mother and two sisters is normal as to the Q T interval the father has a conspicuous bradycardia (50 beats per minute) We placed the boy under treatment with propranolol (80 mg) and, *since then 11* months have elapsed and he remains free from syncopal attacks In this *case* however due to the low frequency of the attacks a *longer* than normal period of time is required to correctly evaluate the effects of the therapy

Case 5 RB (case diagnosed and followed by Dr A Nava Padova Italy) was born on June 9 1967 This girl is deaf mute and started having syncopal attacks when she was 18 months old. She often had several *episodes in* the same day followed by two to three weeks without any attack While she was *continuously* monitored in the coronary unit, several episodes of electrical *alternation* of the T wave (Fig 1 *B*) were observed, often preceding or following ventricular fibrillation This was of the type called par torsades de pointe "[10] The family history shows that a twin sister of a maternal aunt who *herself* has a prolonged Q T interval but no syncopal attacks died suddenly at two years of age It is impossible to correctly evaluate this *episode* Since September 1972 the girl has been treated with diphenylhydantoin (DPH) (120 mg) and *for* one year she remained free from syncopal attacks. In October 1973 she had another attack Practolol (120 mg) was added to her drug *therapy of DPH* In the following eight months she has had no further attacks Her

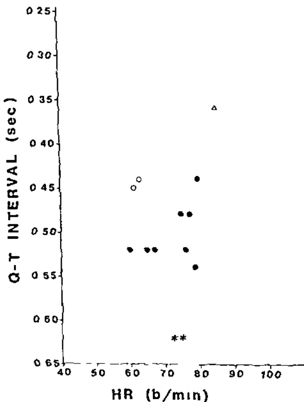


Fig 2 Case 2 Effect of exercise and left sympathectomy on the Q T *interval The shaded* area represents the normal values of Q T interval for a given heart rate • = control *values* = after two exercise tests Δ = two hours after left sympathectomy O = six *and seven* months after surgery

Table I

Author and year	Case	Sex	Deaf ness	First syncope	Therapy	Outcome
Jervell and Lange Nielsen 1957[1]	1	M	+	3 years	None	Death 9 years
	2	F	+	5 years***	None	Death 5 years
	3	F	+	5 years	Dig + Prop	+++ (1974)[17]
	4	F	+	3 years	None	Death 4 years
Gyllensward 1957[18]	5	F	–	2 years	None	?? (1957)
	6	M	–	??	None	Death 5 years
Moller 1957[19]	7	M	+	3 years	Oxygen	?? (1957)
Levine and Woodworth 1958[20]	8	M	+	3 years *	None	Death 13 years
Romano et al 1963[2]	9	F	–	2 months	None	l s o (1973)[21]
	10	M	–	??	None	Death 44 days
	11	M	–	??	None	Death 4 months
Ward 1964[3]	12	F	–	16 months	Carbamazepam and PHB	Death 14 years (1972)[22]
	13	M	–	15 months	Stopped Prop	Death 17 months
Fraser et al 1964[12]	14	F	+	??	None	Death 14 years[23]
	15	F	+	??	None	l.s o
	16	F	+	Never	None	+++
	17	F	+	18 months	None	Death
	18	F	+	??	None	Death 23 years
	19	M	+	??	None	Death 3 years
	20	M	+	??	None	Death 3 years
	21	F	+	??	None	l.s o
	22	M	+	??	None	l.s o
Gamstorp et al 1964[24]	23	F	–	5 35 years*	Potassium	? (1964)
	24	M	–	3 years	None	Death 9 years
Barlow et al 1964 see Gale et al 1970						
Jervell et al 1966[25]	25	F	+	9 years	Dig + Pract (300 mg)	+ (1974)[17]
	26	F	+	4 years	Dig + Pract (300 mg)	+++ (1974)
	27	M	+	2 months	Dig + Prop	+ (1974)
Lisker and Finkel stein 1966[26]	28	M	+	2 years	Belladonna tincture	Death 8 years
Jervell and Sivertssen 1967[27]	29	F	+	18 months	Dig + Pract (300 mg)	+ (1974)[17]
Lamy et al 1967[28]	30	F	+	2 years	Pacing (1973) + Gard	s.a # +++ (1974)[29]
	31	F	+	5 years *	Pacing + Gard	s.a
Bonham Carter 1967[30]	32	M	+	??	??	??
Kallfelz 1968[31]	33	M	+	2 years	None	Death 16 years
	34	M	–	3 years	None	Death 9 years
Tamura et al 1969[32]	35	F	+	??	??	??
Dupuis et al 1969[33]	36	F	+	2 years	Dig	? (1969)
	37	F	+	??	None	Death 1 year
	38	M	?	??	None	Death 3 years
	39	F	?	??	None	Death 1 year
Fauchier et al 1969[34]	40	F	+	3 months	None	??
Van Bruggen et al 1969[35]	41	F	+	2 years	Stopped benemid	Death 8 years
Sanchez Cascos et al 1969[36]	42	F	+	3 months	None	l s o (1973)[37]
Gale et al 1970[38]	43 53	19M	–	??	None	Death
	54 76	15F	–	??	Dig + Prop	+++ (1974)[39]
Combrink 1970[40]	77 84	??	??	??	??	??
Karhunen et al 1970[41]	85	F	–	12 years	ALP (400 mg)	+++# Death 28 years[42]
Lipp et al 1970[43]	86	M	–	14 days	DPH	+++ (1973)[44]
Phillips and Ichinose 1970[45]	87	M	–	11 years	Prop # none	+++ (1974)[46]
	88	M	–	??	None	Death 3 years
	89	M	–	??	None	Death 5 years

?? no information ? no recent information (1968) year of last information 22 years age at death or at time last information received # change of therapy and outcome in successive periods s a syncopal attacks continue + reduction in syncopal attacks +++ suppression of syncopal attacks few attacks in all few attacks per year several attacks per year or per month PHB phenobarbital DPH diphenylhydantoin DIG digitalis GARD gardenal PROP propranolol PRACT practolol ALP alprenolol OXP oxprenolol and l s o lost sight of

Table 1 Continued.

Author and year	*Case*	*Sex*	*Deaf ness*	*First syncope*	*Therapy*	*Outcome*
Olley and Fowler 1970[47]	90	M	+	18 months	Prop (50 mg)	+ (1973) 9 years
	91	M	+	18 months	Prop+DPH+PHB	+ (1973)[48] 13 years
Choussat et al 1970[49]	92	M	+	11 years	Dig	Death, 12 years
	93	M	+	??	None	Death 11 years
	94 98	4M1F	+	??	None	? (1970)
Hashiba et al 1970 and Nakane et al 1971[50]	99 102	??	–	??	??	??
Ruser 1970[51]	103	M	–	3 years	Prop	+++
Nakamura et al 1971[52]	104	F	–	??	??	??
	105	F	–	??	??	??
Dolara et al. 1971[53]	106	F	+	2 years	Luminal	+ 16 years[54]
Garza et al 1971[55]	107	M	–	20 months	None	Brain damage
	108	M	–	4 years	Prop (80 mg)	+++# Death 14 years
	109	F	–	12 years	Prop	+++ (1974) [6]
Wennevold and Kringelbach 1971[57]	110	M	–	9 months	Prop + PHB	+
	111	M	–	2 years	Dig + Prop	Death 3 years[58]
Moss and McDonald, 1971[6]	112	F	–	36 years	Left sympathectomy	+++ (1974) [9]
Ratshin et al 1971[60]	113	F	–	10 years	DPH	1 s o (1974)[61]
Pernot et al. 1972[62]	114	M	+	1 year	Stopped dig + prop	Death 3 years (1973)[63]
	115	F	+	4 months	Dig + prop	+++ (1973)
Hadot 1972[64]	116	F	+	?	None	Death 40 years
Athanasiou, et al 1972a[65]	117	M	–	5 years	Pacing #	s a #
					Dig + isoptin	?
Athanasiou, et al 1972b[66]	118	M	+	10 years	None (last s a 13 years)	+++ (32 years)
Dewitz et al 1972[67]	119	M	–	10 years	Prop	+++ (47 years)
	120	M	–	3 years	Prop	+++ (10 years)
Mathews et al 1972[25]	121	F	–	18 years	Prop (120 mg)	+++ (1974)[68]
	122	M	+	14 years	None (one s a only)	+++ (1974)
	123	M	+	18 years	None	Death 18 years
	124 8	3F2M	1+4–	??	None	+++
Johansson and Jorming 1972[69]	129	M	–	5 years	Pract	+++ (1974) 32 years[70]
	130	M	–	2 months	Pract	+++ (1974) 7 years
Kedra et al 1972[71]	131	F	??	??	Pacing	? (1972)
Gallez 1972[72]	132 141	9F 1M	–	?? 4 Never	None 9 (6 adults)	+++ (1972)
Lubbers 1972[73]	142 147	4F 2M	–	??	Prop 1 ??	+++ ??
Ramon et al 1972[74]	148	F	–	18 months	Right sympathectomy + Pract (250 mg)	Death 3 years
Ruser 1973[75]	149 171	10M 13F	–	??	Prop	+++
Hanazono et al 1973[76]	172	F	–	11 years	Potassium#prop	s a #+++ 21 years
	173	F	–	13 years	Prop+DPH+PHB	+++ 17 years
Van der Straten and Bruins 1973[77]	174	M	+	??	??	??
	175	F	–	3 years	??	??
Caanady and Kiss, 1973[78]	176	F	–	19 years	Prop # OXP	+++ # +++
Froggatt and James 1973[16]	177	F	–	6 years	PHB	Death 9 years
Enrico et al. 1973[79]	178	F	–	15 years	Isoproterenol	?
Cillet and Voegtlin 1973[80]	179	M	+	18 months	Gard	Death 12 years
Vincent et al 1974[81]	180 1	??	??	??	??	??
Langslet and Sorland, 1974[82]	182	M	+	??	Dig + pract	+++
	183	M	+	??	DPH	Death 3 years
Froggatt and Adgey in press[83]	184	M	+	??	None	Death 2 years
Kernohan and Froggatt in press[84]	185	M	??	9 years	??	??
Dear 1974[85]	186	F	–	Infancy	Left sympathectomy	+++ (52 years)
Philips, 1974[46]	187	M	??	??	Prop+DPH+bretylium	Death 14 years
Mathews and Blount, 1974[68]	188	M	+	14 years	Prop (120 mg) + DPH (300 mg)	+++

Table I Continued

Author and year	Case	Sex	Deafness	First syncope	Therapy	Outcome
Karhunen 1974[42]	189	F	–	21 years	Alp+1 Hyoscyamine	+++ (34 years)
	190	F	–	35 years	None	Death
	191	F	–	8 years	Practolol	+++ (18 years)
Johansson 1974[70]	192	M	–	Never (1 year)	None	+++ (son of case 129)
	193	F	+	29 years	??	??
	194	M	+	3 years	None (one s a only)	+++ 33 years
	195	F	–	Youth*	None	+++ 50 years
	196	F	–	27 years	Pract	+++ 36 years
Froggatt 1974[23]	197	M	+	18 months	DPH+mysoline+thoraline	Death 14 years
Schwartz and Malliani 1974[6]	198	F	–	3 years	None	Death 19 years
	199	F	–	3 years	Prop ♦ left	+ ♦
					Sympathectomy + Prop	+++ 13 years
Schwartz, et al this paper	200	F	–	Never (1 year)	None	+++ (sister of 198 9)
	201	M	–	6 years	Prop (80 mg)	+++ 8 years
	202	F	+	18 months	DPH ♦ DPH+Pract	+♦+++ 7 years
	203	F	+	3 years	DPH + PHB ♦ prop + PHB	s a ♦ +++

Q T interval is clearly prolonged (Q T_c 0 54)

Case 6 BD (case followed by Dr G Sell Tennessee) (This case has been briefly mentioned elsewhere[11]) was born on Aug 8 1966 This deaf mute girl started having syncopal attacks when she was three years old Her Q T interval was clearly prolonged (Q T_c 0 51) She had two to three syncopal attacks every year several of them occurring while she was swimming She was treated for four years with phenobarbital (PHB) (80 mg) and DPH (75 mg) but these drugs did not prevent further attacks She was recently referred to us for therapeutic advice and we suggested initiating propranolol therapy at once She is at present taking propranolol (120 mg) and continuing with PHB (60 mg)

Epidemiologic Investigation

We examined the ECG of 375 boys and girls attending schools for deaf mute children in Milan No one was affected by LQTS

Discussion

A great deal of advances have been made in the understanding of the long Q T syndrome, but there are some points which do not require a further detailed analysis here

As to the clinical manifestations the description of the syncopal attacks has been extensively made by Fraser, Froggatt, and James[12] and by Jervell[14] We recently showed that these patients have another characteristic symptom the likelihood to develop brief episodes of alternation of the T wave following the same stimuli which usually trigger the syncopal attacks[6] Several patients have syncopal attacks while swimming or during menses The seriousness of LQTS is not the same in all patients while several patients have many syncopal attacks per month, others have a few per year, and still others have one or two episodes in all their life This point is crucial in evaluating the effects of therapy

The possible mode of inheritance has been largely discussed in several papers[13,15] Each conclusion must, however, take into account the finding of patients with and without deafness in the same family[15] and the frequent lack of any familiarity especially impressive is the case of SC, where, after her death, 342 of her relatives were examined with negative results[16]

Frequency As already suspected by many authors this illness is undoubtedly more unrecognized than rare This becomes clear if one considers that 170 out of 200 diagnosed cases were reported in the last five years indicating that the larger the diffusion of the knowledge of LQTS the higher the number of diagnosed cases To the best of our knowledge all the diagnosed cases of unequivocal LQTS are listed in Table I

While it is at present impossible to know the frequency of the type without deafness, there are increasing data on the form with deafness (Table II) The frequency of LQTS among deaf mute children is about 0 25 per cent *It is noteworthy* that the cases with deafness represent 30 per cent of all the patients affected by LQTS

Pathogenesis The pathogenesis of LQTS is still considered to be unknown Three main hypotheses have, however, been advanced abnormalities in the vascularization of the sinus node[69] in the myocardial metabolism,[3,14,55] and in the effects of adrenergic stimulation[8,47,89] While

the first two hypotheses have few if any supportive data in their favor, there is an increasing and rather definite evidence for a direct relationship between LQTS and the sympathetic nervous system (1) The syncopal attacks are triggered by events like emotions or physical exercise known to increase the sympathetic activity, (2) both the characteristic electrocardiographic signs i e prolongation of the Q T interval and episodes of alternation of the T wave can be reproduced by asymmetrical alterations in the sympathetic tone[6,8] and (3) the best therapeutic results are obtained by antagonizing the effects of sympathetic activity on the heart with beta blocking agents and/or by ablating the left stellate ganglion (LSG) along with the first thoracic ganglia[90]

In experimental studies Yanowitz Preston and Abildskov[7] produced a lengthening of the Q T interval by either stimulating the LSG or ablating the right stellate ganglion (RSG) in dogs we showed that stimulation of LSG not only prolongs the Q T interval but also produces episodes of alternation of the T wave *in cats*[5,6] The clinical observation was made that T wave alternans in addition to the expected Q T prolongation followed the pharmacologic *blockade* of RSG[8] All of these data clearly indicate that some nonhomogeneous asymmetrical cardiac sympathetic innervation is involved in the LQTS and particularly suggest an imbalance between the right and left sympathetic outflows to the heart This hypothesis led to three surgical attempts with left sympathectomy[6,8,65] and their success is a further and particularly important confirmation of the hypothesis itself

At present it is unknown at which level this imbalance takes place (brain sympathetic chain or adrenergic terminals in the myocardium) The experimental results and therapeutic attempts suggest that in the majority of cases at least the sympathetic activity is greater in the left than in the right side (this is, of course a rough over simplification) This could depend either on an increased activity through the left sympathetic nerves or on a decreased activity through the right sympathetic nerves We suggest that the latter may occur more often as a pathogenetic mechanism in the majority of patients affected by LQTS

This hypothesis is based on the abovementioned and on the following considerations Randall and Rohse[91] showed that LSG mediates mainly inotropic effects while RSG mediates mainly chronotropic effects Therefore we would expect that patients with a decreased activity through the right cardiac sympathetic nerves have a slightly lower than normal heart rate (although this may be minimized by vagal compensatory mechanisms) and especially a decreased capability to increase their heart rate Indeed, low heart rates (often less than 60 beats per minute have been reported by a number of authors[12,15,25,26,35,41,45,47,53,57,66,69,73,74,76,80] This is impressive since most of the patients observed were children who would normally have higher heart rates We also investigated in all the reports on LQTS whether some of the patients had been subjected to an exercise test (stimulus known to increase the heart rate of all normal individuals) we found that six[1,26,33,45,49,62] and our Case 2 (a total of seven) out of twelve[3,21,26,41,55] did not increase their heart rates during valid exercise tests The validity of the test is proved by the prolongation of the Q T interval brought about by exercise (Fig 2) This fact would be an exceptional finding for normal individuals but is just what we would expect in patients with a reduced activity through the right sympathetic nerves The apparent lack of vagal withdrawal in these patients is however surprising and may indicate other dysfunctions e g in the sinus node inner

Table II Frequency of the long Q T syndrome among deaf mutes

Authors	*No. of deaf mutes*	*Long Q T syndrome*
Fraser et al.[12]	1 514	9
Puletti et al.[86]	211	0
James[87]	367	0
Dupuis et al[33]	182	0
Sanchez Cascos et al.[36]	511	1
Fay et al[88]	1 126	1
Dolara et al[53]	262	1
Pernot et al[62]	298	1
Gillet and Voegtlin[80]	231	1
Schwartz, et al (this report)	375	0
Total	5 077	14 (0 28%)

This represents the number of ECGs actually recorded, however since it is also the second stage of a screening procedure the ascertainment of nine cases would be out of 2 994 subjects instead of 1 514[13] This would reduce the frequency of LQTS among deaf mutes to 0 21 per cent.

vation It is noteworthy that two[1,62] of those seven patients were also tested with atropine and one[62] of them failed again to increase his heart rate

We are not suggesting that a lower than normal right sympathetic activity is present in all the patients with LQTS Actually it is extremely likely that individual patients have different kinds of local sympathetic imbalance and in some of them, for instance this could involve only a minor portion of the sympathetic terminals The fact that some of the patients may increase their heart rate, Froggatt's[23] observation that in a little patient either right or left stellate ganglion blockade led to a shortening of Q T interval and Ramon's[74] finding that shortening of Q T occurred after right stellate blockade are all data which indicate that great individual variability may be present and that no rigid statements are possible As to the mechanism by which these patients are exposed to a high risk of ventricular fibrillation, it is known that usually, but not always a lengthening of the Q T interval increases the vulnerable period[92] increasing the likelihood that a premature beat could trigger ventricular fibrillation[93] In addition to that, a decreased activity through the right sympathetic nerves represents a condition which favors the development of arrhythmias[94]

However the possibility cannot be ruled out that some local myocardial abnormality might also be involved in the pathogenesis of the disease In such a case the sympathetic interventions would only trigger the syncopal episodes

Pharmacologic blockade of the stellate ganglia (SGB)

Evaluation of SGB This procedure has been used by several authors after the first successful surgical attempt[6] in order to evaluate the possible usefulness of the surgical ablation of one stellate ganglion This procedure, if not critically used may be quite misleading In fact it is a still[95] widely diffused misconception that the appearance of Horner's syndrome is the marker of an effective SGB and therefore of a block of cardiac nerves on the contrary, it only indicates the blockade of the fibers which traverse the upper part of the stellate ganglion It may or may not be accompanied by effective blockade of fibers innervating the heart

The SGB is usually performed through a blind procedure and there can be no certainty about the exact spread of the anesthetic Moreover, this test is too often done with local anesthesia and there is no doubt that such a maneuver will scare normal individuals, resulting in increased sympathetic activity If we are dealing with patients having a nonhomogeneous cardiac sympathetic innervation and if, as is often the case the blockade is not complete it would not be surprising to find paradoxical responses For instance an attempted LSGB could even lead to a prolongation of the Q T interval, but as a result of an increased discharge through the LSG itself In addition, there is always the possibility that the needle on its way could induce a mechanical stimulation of the SG

SGB and LQTS Moss and McDonald[5] obtained a Q T prolongation with RSGB and a shortening with LSGB A left stellectomy was then performed, resulting in a definite shortening of the Q T interval and in the disappearance of the syncopal attacks Three years after the surgery the Q T interval was again prolonged, but the patient s condition is still excellent[59]

Ratshin and co workers found a prolongation of the Q T interval with both LSGB and RSGB On the basis of these results, the surgical therapy was discarded the patient was placed under treatment with DPH discharged from the hospital and subsequently was lost sight of

Froggatt[23] obtained in a child a shortening of the Q T interval with both LSGB and RSGB After some logical and understandable hesitations and an exchange of opinions with James[96] a left sympathectomy was scheduled. The night preceding the surgery the little boy had another syncopal attack and died

Ramon and co workers[74] obtained in their two year old patient a prolongation of the Q T interval with LSGB and a shortening after RSGB The patient was subjected to a right sympathectomy After an extremely short favorable response the situation worsened again, and six months later the girl died

Vincent and co workers[81] had a reduction in the Q T interval after both LSGB and RSGB in two patients although in one case the change after RSGB was minimal

Schwartz and Malliani[6] on the basis of experimental and clinical results performed a left sympathectomy without previous pharmacologic blockade in one of their patients with totally favorable results See case report 2

Dear[85] observed no change in the Q T interval after either LSGB or RSGB Despite these results he performed a left sympathectomy the Q T interval was normalized, and his patient re mained completely free from syncopal attacks during the twenty two months since surgery

These results are somewhat conflicting but not totally unexpected for the reasons mentioned above and because individual variations may in fluence the characteristics of this disease

Ramon s decision to perform a right sym pathectomy was the not illogical consequence of his results with SGB however there is no doubt that at the end of the operation the patient had a sympathetic imbalance with a left prevalence

Dear s case is a clear example of the unreliability of SGB Had he based his decision on the SGB results his patient would not have received the benefit of the left sympathectomy which shortened the Q T interval to normal values and suppressed completely the previously frequent syncopal attacks

Vincent also reports data on the effect of stimulation of the stellate ganglia in two pa tients Unfortunately these possibly interesting data are obscured by the fact that he used a per cutaneous stimulation This procedure has little value since the exact position of the stimulating electrode was unknown Furthermore as the result of current spread, the stimulation could not be selective His SGB are also difficult to evaluate he states that in one patient RSGB shortened the Q T interval and led to an increase in heart rate of 25 beats per minute It would follow that the right stellate ganglion has a tonic inhibitory influence on the sinus node which is difficult to accept A mechanical stimulation of RSG through the tip of its needle could be an alternative explanation

Despite the limitations just listed, the shorten ing of the Q T interval following RSGB at least in some cases is a fact and cannot be overlooked.

Diagnosis. The association of a prolonged Q T interval and syncopal attacks following emo tional or physical stresses represents a dramatic and unmistakable clinical picture If congenital deafness and/or episodes of alternation of the T wave occur the diagnosis is even easier

Unfortunately sometimes confusion is made between LQTS which is congenital and the so called acquired long Q T syndrome The latter described by Motte and co workers[87] is charac terized by the occurrence of syncopal attacks due to ventricular fibrillation independent of emo tional states or physical exertion and by the fact that the prolongation of the Q T interval is al ways *secondary* to conditions like A V block sinus bradycardia (45 to 50 beats per minute) hy popotassemia or use of drugs like quinidine phenothiazine imipramine amiodarone and others The patients affected by the acquired form are usually first seen in their fifth or sixth decades and ECG tracings of their childhood, when available do not show any prolongation of the Q T interval

The distinction between these two conditions which have in common the prolongation of the Q T interval and the likelihood of syncopal attacks is of great importance because due to their totally different pathogenetic mechanisms their therapies are obviously totally different In fact in the acquired form a diffuse myocardial de synchronization is responsible and antiar rhythmic drugs such as propranolol are ab solutely contraindicated, the therapy of choice for these patients being the ventricular pacing

The aforementioned confusion (also in a very recent article on LQTS[95] cases of the two forms are listed together) led, in fact especially in Italy and Spain to the appearance of several articles concerning alleged cases of congenital LQTS while the patients reported clearly had an ac quired form Moreover this confusion prevented some patients affected by LQTS from receiving the treatment with beta blockers and induced their doctors to use therapies indicated for the acquired form of the long Q T syndrome

At present there are no elements to define the possible and likely relationships between LQTS and the syndrome of familial ventricular fibrilla tion (usually following emotional or physical stresses) with a normal Q T interval described by various authors[98-101] The following points seem however worthy of mention (1) some of these pa tients have an abnormal U wave and in LQTS the T wave abnormality is often a T U abnor mality (2) some of these patients increased their Q T with physical exercise to pathologic values and this unusual response is also characterically present in LQTS (3) according to the cancella tion theory[102] a high degree of cancellation dur ing repolarization permits large alterations of recovery times in areas that are self cancelling to have very little effect on T wave form The op

Table III Effects of therapy on the long Q T syndrome mortality*

	Total	Outcome unknown	Deaths (%)
Patients with LQTS	203	47	53 (34%)
Patients without *syncopal attacks*	7	/	0
Treatment unknown	28	28	
Not treated	68	12	41 (73%)
Treated without beta blockers	18	7	7 (64%)
Treated with beta blockers	79	/	5 (6%)
Left sympathectomy	3	/	0

This table has only an indicative value and it must be realized that it has several limitations (1) the table lists together patients affected by LQTS of different degrees of seriousness (2) the dosage of beta blockers is not the same with different patients (3) several patients in the not treated group had very few syncopal attacks in their childhood and they are now adults (4) some patients were followed for more than ten years while others only for a few years (5) treatments different from beta blockers are grouped together However since the data are collected from all the known patients to our best knowledge we believe that they are fairly representative and highly suggestive of the real value of the treatment with beta blockers compared to different treatments or to no treatment at all

posite, namely, alterations of recovery times in areas that are highly uncancelled is likely to happen in LQTS The mechanism, however could be the same just involving different areas of myocardium

Should a patient affected by LQTS need the surgical therapy, two preliminary procedures could help in deciding which SG has to be removed (1) Although up to now there are no available data on patients with LQTS it could be possible that if the imbalance is in the central nervous system (CNS) and not in the heart itself the sympathetic vasoconstrictor tone in the upper extremities could be asymmetric, too If this were the case, a plethysmography, correctly executed according to Burch,[103] could reveal a different degree of vasoconstriction in the right versus the left hand. (2) As discussed above SGB performed in a blind way is often unreliable Since after the failure of medical treatment there is no alternative to the surgery, it seems rational to perform SGB under general anesthesia just before the ablation of a SG It is suggested that, unless the plethysmography gives different indications, LSG should be approached first Should LSGB under these conditions show no change in the Q T interval, then it will be logical to test the right one

Therapy Any correct therapeutic approach is the logical consequence of the understanding of the pathogenesis of a given illness The LQTS is characterized by syncopal attacks provoked by abrupt increases in the sympathetic activity which is likely to be nonuniform and mostly mediated through the left sympathetic upper thoracic ganglia It follows as already suggested,[90] a double therapeutic line one less specific consisting of the treatment with beta blockers, and one more specific consisting of the ablation of LSG along with the first thoracic ganglia Despite the fact that these therapies seem rational, there is only one way to assess their validity, namely to evaluate the effects of any therapy used in ALL the patients affected by LQTS This unusual therapeutic evaluation was made possible by the limited number of patients and by the cooperation of many authors

Table I lists all the available data concerning these points, and Table III lists the mortality rate in respect to various therapies It must be stressed, however, that there are still several limitations for a correct evaluation of the data (1) some patients were reported 10 to 15 years ago and others very recently It is obvious that the first group being exposed for a longer period of time to syncopal attacks also had greater chances to die (2) In some cases, the reports were published a few months after the beginning of a therapy and positive results were claimed Unless there is further information on these pateints it is difficult to safely assess the outcome Moreover, often patients die after the publication of the case but no one writes a paper just to say that his patient died (3) Some patients, especially in the nontreated group, had one or two attacks in all their life and are now adults likely to have normal lives They clearly have a mild form of LQTS however, their presence in the Tables influences the mortality in the nontreated group which otherwise would be still greater (4) Sometimes beta blockers were used at less than full blocking dose, especially if they were associated with other drugs (5) The number of patients treated with drugs different from beta blockers seems low This depends on the fact that many of these patients continued having syncopal attacks and were finally treated with beta blockers

With these limitations in mind, the following main conclusions may be reached by examining Tables I and III

(1) The patients not treated have a very poor prognosis (mortality rate 73 per cent)

(2) The patients treated with drugs other than beta blockers have a mortality which is only slightly reduced (64 per cent) and if many patients had not been placed under therapy with beta blockers the mortality in this group would probably have been higher

(3) Beta blockers clearly reduce the mortality rate (6 per cent) They are effective in the majority of patients provided that a full blocking dose is used. In the greater number of patients the syncopal attacks are completely suppressed, while in all the others they are greatly reduced in frequency

(4) In the patients whose medical treatment achieved only a reduction of syncopal attacks the left sympathectomy completely suppressed the attacks and shortened the Q T interval (three cases out of three)

As to beta blockers some more observations have to be made Since propranolol is rapidly metabolized, it is crucial that the drug be taken at regularly spaced times It must be clear that *skipping one or two days* in the treatment could jeopardize the patient s life Some of the few deaths in patients taking propranolol occurred the very next day after propranolol was stopped or the patient failed to take the drug the day of the fatal attack To check the propranolemia[9] regularly could be useful To use low dosages is useless There should be no hesitation in increasing the beta blocker dosage to reach an effective blockade Usually these patients *in spite of* a low resting heart rate tolerate high doses very well however should a bradycardia ensue the problem could be solved by adding l hyoscyamin as suggested by Karhunen[42] The patients in whom full doses of beta blockers produce side effects are the ones for whom we suggest adding diphenylhydantoin (DPH)

DPH proved to be effective in some patients As to its mode of action in addition to its antiarrhythmic properties DPH diminishes synaptic transmission in the stellate ganglia[104] and this is highly suggestive in regard to the proposed pathogenetic mechanism of LQTS

Digitalis has been employed in several patients but clear favorable results have been obtained only when it was associated with beta blockers We believe that in these patients the beneficial effect is dependent on beta blockers alone

Especially in dealing with hyperexcitable patients the use of phenobarbital is advised[95] and, associated always with beta blockers seems sound

Despite the fact that the association of beta blockers with other drugs could sometimes be useful or even necessary this has resulted too many times in the use of a low dosage of beta blockers with lack of complete beta blockade and poor results

The extremely favorable results obtained by the left stellectomies are highly encouraging but this should by no means lead to a mass stellectomy It is evident that a number of patients are able to carry on a normal life with the complete suppression of the syncopal attacks using adequate doses of beta blockers However, should the treatment with beta blockers be followed only by a reduction and not by the elimination of syncopal attacks then considering that any of these episodes may prove fatal we believe that surgical treatment is the most rational choice If the diagnostic measures suggest a right sympathectomy we would, instead, favor a *bilateral* one to avoid creating the dangerous imbalance with left prevalence Should the left sympathectomy fail in individual cases the more correct solution seems to be represented by a total ventricular denervation using the peripulmonary neurectomy technique according to Kay[105]

Since it is now possible for the correctly treated patients to escape death the existence of undiagnosed cases is inexcusable The diffusion of the knowledge on the long Q T syndrome among not only the cardiologists but also pediatricians neurologists and moreover, general practitioners and medical students becomes an imperative and easy social measure

Summary

Recent clinical and experimental data on the long Q T syndrome (LQTS) are presented and discussed. The pathogenesis of LQTS is dependent on an imbalance between various components of the cardiac sympathetic innervation A congenital decreased activity through the right cardiac

sympathetic nerves seems to be the more likely pathogenetic mechanism for the majority of cases Other forms of sympathetic imbalance, including left or even right hyperactivity, are, however, possible in isolated cases

Beta blockers, at full blocking dose represent the therapy of choice and are greatly effective in reducing the mortality (from 73 per cent to 6 per cent) If syncopal attacks are not eliminated by the medical therapy, then the ablation of the left stellate ganglion along with the first thoracic ganglia is the most rational and specific therapy The possibility for the correctly diagnosed and treated patients to escape an otherwise impending death calls urgently for diffusion of the knowledge about the long Q T syndrome

Addendum

Since preparation of this review, more data have become available Case 185 was published (see Ref 84) This 10 year old boy is being treated with atropine and continues to have syncopal attacks Schneider and associates (Z Inn Med Jahrg **19** 418, 1974) reported six cases three of them are all right with propranolol two were without treatment and one died and one had treatment different from beta blockers and died. Singer and associates (Arch Neurol **31** 64 1974) reported one case favorably treated with bretylium tosylate Bonham Carter had two new cases [23] Dr R Pryor (University of Colorado, Denver) informed us about three cases two of them died without therapy one is doing well with propranolol Dr P Willis (University of Michigan, Ann Arbor) informed us about seven cases three are all right with beta blockers + PHB, one died with no treatment two are all right with no treatment (one however, never had syncopal attacks (S A) and one had only one S A) His seventh case deserves special consideration a 28 year old woman had several S A (documented as ventricular fibrillation (VF)) which in the last three weeks became dramatically frequent (1 to 2 every day), on the basis of the data presented here a left stellectomy was performed Only 10 days have elapsed since surgery meanwhile however the patient remains completely free from S A These data increase to 220 the number of patients to our knowledge It is interesting to note that the percentages reported in Table III are practically unmodified

Meanwhile, experimental data bearing an important relationship to LQTS have been obtained (P J Schwartz, N G Snebold, and A M Brown, submitted for publication) Briefly, the ablation of the right stellate ganglion resulted in a significant decrease in the ventricular fibrillation threshold (VFT), which means an increased vulnerability to VF If the patients with LQTS do really have, as we suggest, a congenital decreased activity through the RSG then they will also have a VFT lower than normal This explains why, under conditions of increased sympathetic discharge not harmful to normal individuals, they easily go into VF By striking contrast, ablation of the left stellate ganglion greatly increases the VFT This protective effect may well account, in addition to the shortening in Q T interval, for the successful results obtained by this procedure and increase the rationale for this therapy

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Appraisal and reappraisal of cardiac therapy

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Electrophysiology and pharmacology of cardiac arrhythmias IV Cardiac antiarrhythmic and toxic effects of digitalis

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The clinical effects of digitalis and the biochemical and electrophysiologic basis for its action have been the subject of a number of recent reviews [1-4] Despite the extensive investigation of the actions of digitalis there are still many questions concerning the mechanisms underlying its therapeutic and toxic effects Our intent in this review is to describe the current state of knowledge concerning the electrophysiologic mechanisms which determine digitalis effect, and to indicate those areas where uncertainty still exists In keeping with the purpose *of this series of* reviews our discussion of the therapeutic and toxic effects of digitalis will be confined largely to those actions which may suppress or induce cardiac arrhythmias

Therapeutic effects of digitalis

Most if not all of the antiarrhythmic effects of digitalis are the result of its action on the atria and atrioventricular junction These therapeutic effects are part of a complex series of interactions involving digitalis the autonomic nervous system and the cardiac cells The electrophysiologic changes induced by digitalis in the in situ heart are a slowing of sinus rate a variable degree of enhancement of intra atrial conduction depression of atrioventricular conduction and prolongation of the atrioventricular nodal *effective* refractory period.[5] The actions at the atrioventricular node are largely responsible for the utility of digitalis in slowing ventricular rate during atrial flutter or fibrillation

The sinus slowing which accompanies digitalis therapy has been attributed to both a direct effect of the drug on impulse initiation by the sinus pacemaker cells and a cholinergic action mediated by the vagus nerve [5] However, most studies suggest that the latter is the more important of the two mechanisms For example Toda *and West*[6] reported no change in action potential amplitude or maximum diastolic potential of cells in the region of the rabbit sinus node following perfusion with ouabain 2×10^{-7}M Studies by Ten Eick and Hoffman[7] revealed that sinus slowing induced by ouabain 4×10^{-7}M could be blocked by atropine The studies of Toda and West[6] suggest there is little direct effect of therapeutic ouabain concentrations on sinus node cells Those of Ten Eick and Hoffman[7] indicate that any effects that ouabain exerts on the sinus *node may* be diminished by cholinergic blockage

Other studies have provided additional support for the involvement of the autonomic nervous system in mediating digitalis induced sinus slowing Heymans and associates[8] using dogs with chronic baroreceptor denervation and Krayer[9] in studies of cross perfused canine hearts demonstrated that for ouabain to slow sinus rate vagal afferent and efferent pathways had to be intact Ten Eick and Hoffman[10] found that ouabain increases the number of fibers in the sinus branch of the vagus that respond to a constant strength

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stimulus They suggested that ouabain enhances vagal excitability and may thereby potentiate vagally induced sinus slowing Digitalis has also been shown to enhance ganglionic transmission[11] and to increase the sensitivity of the sinus node to exogenous acetylcholine[6] All of these studies, then, indicate a strong association between the parasympathetic nervous system and the effects of digitalis on sinus rate

The adrenergic nervous system, too, has been studied with respect to digitalis effects on cardiac rate Digitalis has been shown to decrease the sensitivity of the sinus node to sympathetic stimulation or β adrenergic amines, thereby tending to slow cardiac rate[12,13] The anti adrenergic and cholinergic effects of digitalis then, are complementary, both serving to decrease the rate of impulse initiation in the sinus node

Digitalis has a variable effect on conduction in the atrium This results from its direct actions on atrial myocardial and specialized conducting cells and its interactions with the cholinergic nervous system[5] The indirect effect induces an increase in acetylcholine release and an apparent enhanced sensitivity to this neurotransmitter[5] Acetylcholine increases the potassium conductance of the cell membrane, an effect which results in hyperpolarization of atrial myocardial and specialized conducting cells and attendant increases in action potential amplitude and $\dot{V}_{max}$[14] These effects are most prominently seen in the presence of low digitalis concentrations, and are associated with enhancement of conduction Additional changes seen are an acceleration of repolarization and shortening of the atrial effective refractory period[5]

Higher digitalis concentrations partially depolarize atrial cells and depress conduction[5] by a direct action similar to that which occurs in the ventricle This will be described shortly Atropinization of atrial tissues will also serve to counteract the cholinergic actions of digitalis resulting in variable degrees of depolarization, slowing of conduction, and prolongation of atrial action potential duration and the effective refractory period[15]

In the atrioventricular node the effect of digitalis is to slow conduction and prolong the effective refractory period The prolongation of the effective refractory period appears to occur at digitalis concentrations that do not otherwise modify the nodal action potential[16] In great part, this change may be a result of the combined cholinergic and antiadrenergic actions of digitalis The direct actions of digitalis on atrioventricular nodal cells also can induce a time dependent prolongation of the nodal refractory period[5] Toda and West[8] demonstrated direct effects of digitalis on the rabbit atrioventricular nodal action potential at ouabain concentrations greater than 2×10^{-7}M These included decreases in maximum diastolic potential, action potential amplitude and phase 0 rate of rise These actions of digitalis on nodal cells were associated with slowing and block of atrioventricular transmission

Summarizing the antiarrhythmic effects of digitalis on the atrium and atrioventricular junction, it is apparent that largely through interactions with the autonomic nervous system digitalis can slow sinus node impulse initiation, hyperpolarize cells in the atrium and enhance intra atrial conduction, slow atrioventricular conduction and prolong the atrioventricular nodal effective refractory period The actions of digitalis on atrial specialized conducting cells — specifically the hyperpolarization and decrease in the slope of phase 4 that occur — would be consistent with a slowing or suppression of ectopic impulse initiation by atrial pacemakers competing with the sinus node and probably explain, in part the successful results seen when digitalis is used in the treatment of atrial tachycardias Similarly, by enhancing intra atrial conduction and modifying refractoriness, digitalis may alter propagation through re entrant pathways in the atrium The prolongation of atrioventricular nodal refractoriness is largely responsible for the slowed ventricular response that occurs when digitalis is used in the therapy of atrial flutter or fibrillation Because atrioventricular nodal refractoriness is prolonged and impulse conduction is slowed rapidly occurring atrial impulses are prevented from propagating to the ventricle with the same frequency that occurs prior to digitalis action at the atrioventricular junction These effects of digitalis on the atrium and atrio ventricular junction provide a basis for the therapy of supraventricular tachycardias and re entry associated with pre excitation as well as for atrial flutter and fibrillation

Although the mechanisms underlying digitalis effect on the atrium and atrioventricular junc

tion are complex there is little doubt that the drug does modify arrhythmias occurring in these regions through both autonomic and direct actions There is no convincing evidence for any similar antiarrhythmic effect of digitalis on the ventricle To be sure digitalis administration in instances where ventricular arrhythmias complicate congestive heart failure often results in remission of the arrhythmias as failure diminishes It is likely however that normalization of cardiac rhythm here is largely a reflection of decreasing cardiac size improved perfusion and normalization of electrolytes and acid–base balance

The cholinomimetic effects of digitalis appear to have no significant role with regard to digitalis action on the ventricle There is little evidence for parasympathetic innervation of the ventricular specialized conducting system nor are there indications that digitalis through cholinergic mechanisms might modify impulse initiation or propagation in the ventricle [17] Similarly digitalis appears to have no antiadrenergic effect on the ventricle

Rather both digitalis[18] and catecholamines[19] tend to increase the slope of phase 4 depolarization in cells of the specialized conducting system Under appropriate conditions these actions could be complementary and lead to ectopic impulse initiation

Probably the only direct effect of therapeutic concentrations of digitalis on cells of the ventricular myocardium and specialized conducting system is a small and somewhat variable prolongation of the voltage–time course of repolarization [20] This prolongation has been attributed to an increase in membrane resistance to potassium ion flux which occurs following perfusion with low concentrations of digitalis [5,20] With prolonged perfusion periods (or higher digitalis concentrations) membrane resistance decreases and repolarization is accelerated.[20] There is evidence that the prolongation of action potential duration induced by digitalis coincides with clinical digitalis effects Recent studies of Purkinje fibers superfused with the blood of intact dogs and therefore receiving the same concentrations of ouabain as the intact dogs have indicated that the prolonged repolarization phase of the action potential occurs concurrently with ouabain induced changes in the electrocardiographic ST segment and T wave [21] It must be stressed, however that this change in the action potential is unassociated with any demonstrable antiarrhythmic effect The subsequent acceleration of repolarization induced by digitalis is apparently a toxic effect of the drug and will be discussed in the next section

Digitalis toxicity I Direct effects of digitalis on the cardiac cell

A Effect of digitalis on the action potential As mentioned above prolonged perfusion with low concentrations of digitalis or shorter perfusion with higher concentrations speeds repolarization This effect which occurs earlier in fibers of the specialized conducting system than in those of the myocardium [5] has been attributed to a decrease in membrane resistance [20] Other toxic manifestations of digitalis include a decrease in resting membrane potential action potential amplitude and V_m [2] In a recently reported study Rosen and colleagues[21] correlated the electrophysiologic changes resulting from digitalis toxicity with associated alterations in the transmembrane action potentials of Purkinje fibers superfused with the blood of intact animals The occurrence of digitalis induced ventricular tachycardia in the blood donor animals was associated with decreases in Purkinje fiber action potential amplitude to 80 per cent of control V_m to 54 per cent of control and action potential duration to 84 per cent of control An example of these studies is shown in Fig 1 These alterations in action potential amplitude and V_{max} (and concomitant decreases in resting membrane potential) induced by digitalis are associated with depression of conduction in the Purkinje system and may be responsible for certain of the arrhythmias induced by digitalis

Although the alterations in action potentials induced by digitalis were initially attributed to changes in membrane resistance [20] more recent studies have suggested an additional mechanism may be involved that is the binding of digitalis with ($Na^+ + K^+$) ATPase and resultant interference with active transport [23] Such binding has the effect of depleting intracellular potassium concentration increasing intracellular sodium concentration and modifying the concentration gradients for these ions across the cell membrane The depletion of intracellular potassium and/or an increase in the extracellular potassium concentration would modify the

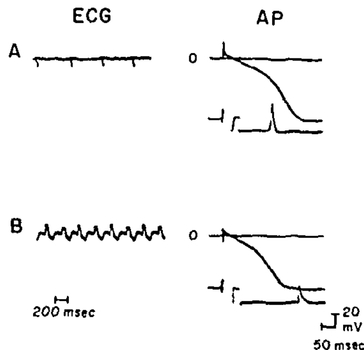


Fig 1 Electrocardiographic and cellular electrophysiologic effects of digitalis *Panel A* is a control showing the electrocardiogram of an anesthetized dog in normal sinus rhythm on the left and the action potential of a Purkinje fiber superfused with the blood of the intact dog on the right Pictured under the action potential is a 200 V/sec calibration and the electronically differentiated V_{max} of phase 0 *Panel B* demonstrates the effects of a toxic dose of ouabain (60 μg/kg) administered intravenously to the donor animal On the left the electrocardiogram shows ventricular tachycardia On the right the action potential shows a decreased resting membrane potential action potential amplitude and V_{max} and an acceleration of repolarization Stimulus cycle length for the Purkinje fiber 500 msec temperature 37 C Elapsed time between panels *A* and *B* 30 minutes (Modified from Rosen Gelband and Hoffman Correlation between effects of ouabain on the canine electrocardiogram and transmembrane potentials of isolated Purkinje fibers Circulation 47 65 1973)

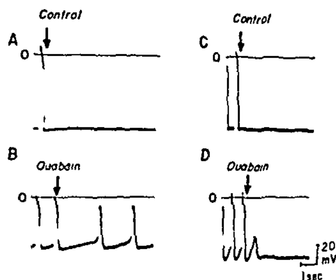


Fig 2 Digitalis induced changes in phase 4 depolarization *Panels A* and *C* controls showing two different Purkinje fibers superfused with Tyrode solution The drive stimuli are discontinued at the arrows followed in both panels by electrical quiescence *Panels B* and *D* were recorded following 35 minutes of superfusion with ouabain 2 × 10 ^{7}M Phase 4 depolarization is occurring in both fibers In *B* discontinuation of the drive *(arrow)* is followed by the onset of a spontaneous rhythm at a cycle length longer than the basic drive In *D* discontinuation of the drive *(arrow)* is followed by a delayed afterdepolarization (see text) and subsequent electrical quiescence Drive cycle length 1000 msec temperature 37 C Tyrode $[K^+]_o$ = 2 5 mM in *A* and *B* 4 0 mM in *C* and *D* (Modified after Rosen Gelband Merker and Hoffman Mechanisms of digitalis toxicity effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potentials Circulation 47 681 1973)

$[K^+]_i/[K^+]_o$ ratio and decrease resting membrane potential This change, in turn, results in decreases in action potential amplitude and V_{max}, slowing of conduction, and acceleration of repolarization Studies with labeled potassium ions indicate that digitalis does decrease the intracellular potassium concentration [24,25] However, this finding has not been uniform in all studies,[26] and the occurrence and extent of digitalis induced changes in transmembrane ionic gradients requires further investigation

B Effect of digitalis on automaticity Digitalis not only modifies the transmembrane action potential, but induces alterations in the slope of phase 4 depolarization of cells of the specialized conducting system [22] The increase in the slope of phase 4 may result in the attainment of threshold potential and a spontaneous rhythm or in a transient sequence of oscillations of membrane potential and subsequent electrical quiescence The latter event has been described for atrial[27] and ventricular[2,28-31] specialized conducting cells and referred to as a low amplitude potential,[21] a transient depolarization [29] or enhanced diastolic depolarization [30]

The changes in phase 4 depolarization induced by ouabain are shown in Fig 2 Panels *A* and *C* are controls showing records from two different Purkinje fibers superfused with Tyrode solution In both discontinuation of the drive stimulus *(arrow)* was followed by electrical quiescence There was no phase 4 depolarization Ouabain was then added to the perfusate, and induced phase 4 depolarization of both Purkinje fibers (*B* and *D*) In *B* discontinuation of the stimulus was succeeded by a stable spontaneous rhythm at a slower rate than the drive In *D*, however, discontinuation of the stimulus was succeeded by a subthreshold depolarization succeeded by

repolarization and no further electrical activity

As mentioned the type of oscillation depicted in Fig 2D has been referred to in the recent literature as a low amplitude potential [21] transient depolarization [29] or enhanced diastolic depolarization [30] In these recent investigations the oscillatory phenomena were digitalis induced Review of the literature indicates that oscillatory phenomena may occur not only as a result of digitalis perfusion [32] but in instances where Purkinje fibers have been depolarized partially by a variety of mechanisms [33] Recently oscillations or afterdepolarizations have been described in slow cardiac fibers—i e those in which depolarization has occurred to the extent that the normal mechanism for phase 4 depolarization and the fast inward sodium current are inactivated and only the slow response and its accompanying automaticity remain [34]

The oscillations described above have in common the fact that they occur following completion of action potential repolarization in cells that have low resting and maximum diastolic potentials As an alternative to the nomenclature recently used to describe these oscillations Cranefield has suggested that the term delayed afterdepolarization" be adopted (P F Cranefield personal communication) This not only is appropriately descriptive of the oscillatory events that occur during phase 4 but distinguishes them from those oscillations which may occur prior to full repolarization and hence are designated early afterdepolarizations

Under appropriate circumstances digitalis induced delayed afterdepolarizations can attain threshold potential and initiate spontaneous action potentials [29,31] The most obvious initiating circumstance is the cycle length of the basic drive As this decreases and the cardiac rate increases so does the magnitude of the delayed afterdepolarizations Similarly if premature action potentials are induced the shorter their coupling interval the larger the magnitude of the delayed afterdepolarizations When an appropriate coupling interval or stimulus rate is attained, then the afterdepolarization will reach threshold and initiate a variable number of spontaneous action potentials as shown in Fig 3

A comparison of the electrical activity in Fig 3 where delayed afterdepolarizations attain threshold and result in a variable number of propagated action potentials and in Fig 2B where

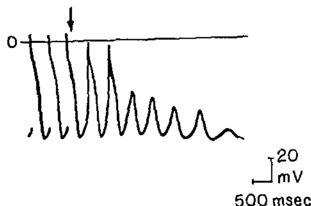


Fig 3 Initiation of spontaneous rhythms by delayed after depolarizations. Purkinje fiber superfused with ouabain 2×10^{-7}M for 25 minutes Basic drive (cycle length 500 msec) discontinued at arrow This is succeeded by two spontaneous beats followed by a succession of delayed afterdepolarizations gradually decreasing in magnitude Temperature 37 5 C (Rosen M R and Merker C)

cessation of the drive results in an escape rhythm, suggests that two rather different types of automaticity may occur as the result of digitalis toxicity The type of rhythm seen in panel 2B is akin to the ventricular escape rhythms that occur clinically in instances where atrioventricular block has occurred. In a recent study we have reported that for isolated tissues such escape rhythms were most readily induced when the Purkinje fibers in addition to being treated with toxic ouabain concentrations were either intentionally damaged (due to stretch) or superfused with a low potassium Tyrode solution [28] Normal fibers superfused with Tyrode having $[K^+]$ = 4 to 5 5 mM were much less prone to develop such escape rhythms and on occasions when they did, spontaneous rate was quite slow However these same tissues usually did develop prominent delayed afterdepolarizations

The clinical corollary of these observations concerning the occurrence of ventricular escape rhythms may be seen in the studies of Smith and Willerson [35] They observed that if patients with cardiac disease took excessive amounts of digitalis the atrioventricular block that developed was usually accompanied by a ventricular escape rhythm However if individuals with healthy hearts took large quantities of digitalis (either accidentally or in a suicide attempt) atrioventricular block was not associated with a comparable ventricular escape mechanism Hence both clinically and in the laboratory it appears that the condition of the fibers in the

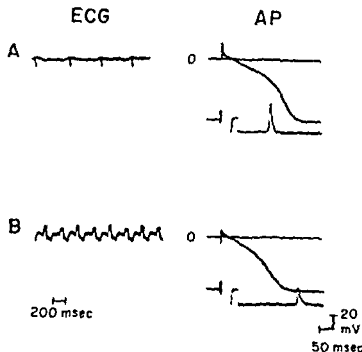


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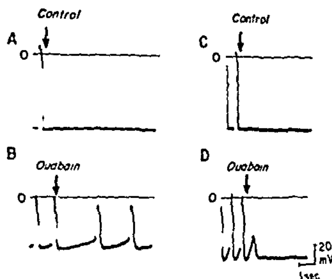


Fig 2 Digitalis induced changes in phase 4 depolarization. *Panels A* and *C* controls showing two different Purkinje fibers superfused with Tyrode solution The drive stimuli are discontinued at the arrows followed in both panels by electrical quiescence *Panels B* and *D* were recorded following 35 minutes of superfusion with ouabain 2×10^{-7}M Phase 4 depolarization is occurring in both fibers. In *B*, discontinuation of the drive *(arrow)* is followed by the onset of a spontaneous rhythm at a cycle length longer than the basic drive In *D* discontinuation of the drive *(arrow)* is followed by a delayed afterdepolarization (see text) and subsequent electrical quiescence Drive cycle length 1000 msec temperature 37 C Tyrode $[K^+]_o$ = 2 5 mM in *A* and *B* 4 0 mM in *C* and *D* (Modified after Rosen Gelband Merker and Hoffman Mechanisms of digitalis toxicity effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potentials Circulation 47 681 1973)

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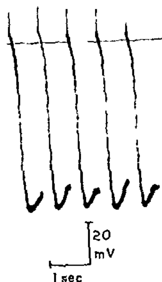


Fig 4 Variation in magnitude of delayed afterdepolarizations in successive cardiac cycles Purkinje fiber superfused with ouabain 2×10^{-7}M for 32 minutes The magnitude of the delayed afterdepolarization varies from one cycle to the next resulting in variations in the level of membrane potential at which successive action potentials are initiated and in the amplitude of the action potentials Temperature 37 C Cycle length 630 msec (Modified after Rosen Gelband Merker and Hoffman Mechanisms of digitalis toxicity effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potentials Circulation 47 681 1973)

the resulting decrease in action potential amplitude and V_{max} are accompanied by a predictable slowing of conduction [43] Since the slope of phase 4 depolarization usually is the same from one cycle to the next the conduction velocity of each action potential similarly does not vary The occurrence of delayed afterdepolarizations however presents a more complex picture This is so because the magnitude of the afterdepolarizations tends to vary somewhat from cycle to cycle resulting in different membrane potentials for initiation of successive action potentials (Fig 4) Associated with these changes in membrane potential are variations in action potential amplitude V_{max} and conduction velocity from one cycle to the next The magnitude of the conduction changes that occur becomes greater if cycle lengths are inconsistent as when premature depolarizations occur An example of this is shown in Fig 5 For each panel the preparation is being driven at the same basic cycle length However a premature depolarization is induced at successively shorter coupling intervals in panels *A* through *D* In *A*, at the longest coupling interval the premature response is initiated when depolarization due to the afterdepolarization is maximum As a result the amplitude of the premature response is reduced and it does not propagate to the myocardium In *B* where the premature response occurs at a shorter coupling interval it occurs before the peak of the afterdepolarization both basic drive action potentials and the premature response arise at similar levels of membrane potential all propagate to the myocardium In *C* at a still shorter coupling interval the first driven response and the premature action potential both propagate The sec

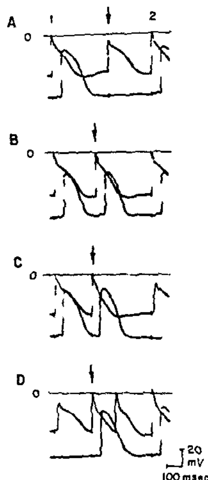


Fig 5 Effects of delayed afterdepolarizations on propagation In panels *A* through *D* *1* and *2* represent the basic drive cycle (700 msec) the arrow indicates a prematurely induced action potential The upper trace in each panel is a Purkinje fiber action potential the lower trace an action potential recorded from the distal ventricular myocardium All panels were recorded within a 4 minute sequence starting 28 minutes after onset of superfusion with ouabain 2×10^{-7}M See text for discussion Temperature 37 C (Rosen M R and Merker C)

Purkinje system influences the type of response that arises in the ventricle when normal cardiac activation is modified by digitalis

The type of automaticity demonstrated in Fig 3, in which delayed afterdepolarizations attain threshold potential and initiate action potentials, is similar to that originally demonstrated for the in situ heart by Lown and associates,[36,37] and referred to as the repetitive ventricular response (RVR) RVR s are single or multiple ventricular depolarizations which result from the electrical induction of a single premature depolarization in the digitalized heart The duration of the train of ventricular depolarizations (actually ventricular tachycardia) induced in this situation has been related to the extent of digitalis overdosage the greater the digitalis overdose, the longer the tachycardia persists The stimuli needed to induce RVR in the digitalis toxic heart are of insufficient magnitude to result in the attainment of threshold potential in the undigitalized heart

These observations with regard to RVR in the in situ heart are comparable to observations concerning delayed afterdepolarizations in isolated Purkinje fibers As with RVR, the stimulus necessary to bring an afterdepolarization to threshold potential is smaller than that required for the fiber not treated with digitalis[29] Also delayed afterdepolarizations evoked by premature depolarizations are more likely to attain threshold—due to their large magnitude—than those which occur at a longer constant cycle length The ability of delayed afterdepolarizations to induce a threshold depolarization and resultant propagated action potential is akin to the induction of RVR by an electrically induced premature ventricular depolarization

The two types of automaticity which appear to complicate digitalis toxicity are not mutually exclusive Whereas, in the laboratory, the escape type of rhythm appears more readily following tissue damage or in the presence of low $[K^+]_o$ and the delayed afterdepolarization in normal tissues at normal $[K^+]_o$, there is some overlap between the two phenomena and both may coexist at times in the same tissue For example, following evocation of delayed afterdepolarizations and a burst of rapidly occurring spontaneous action potentials, there may be a period of electrical quiescence succeeded by the onset of a slow, regular spontaneous rhythm

The similarity or dissimilarity of the electrophysiologic and ionic mechanisms responsible for these two types of behavior is uncertain In normal cardiac fibers, phase 4 depolarization and resultant automaticity are thought to result from an outward potassium current, designated ik_2 [33] that diminishes during phase 4, and a persistent, small inward sodium current[39] It has been suggested that the increase in membrane resistance responsible for initial prolongation of the action potential might also decrease the outward potassium current during phase 4 and cause an increased slope of diastolic depolarization[20] While a decrease in ik_2 may be responsible for changes in the slope of phase 4 induced early in the course of digitalis administration, studies by Hauswirth and colleagues[33] indicate this mechanism is of questionable significance with respect to changes that occur with greater degrees of toxicity They reported that at membrane potentials greater than approximately −65 mV the steady diminution of the outward potassium current, ik_2 is responsible for Purkinje fiber automaticity However, at membrane potentials less than −65 mV, a situation analogous to that in which digitalis toxicity has depolarized the cell automaticity or oscillatory activity could not be attributed to ik_2 These results suggest that a current other than ik_2 may be responsible for digitalis induced delayed afterdepolarizations and changes in the slope of phase 4

In support of this interpretation are experiments concerning the effects of manganese ion[40] and verapamil,[41] both of which interfere with inward currents carried by calcium ion[42] Manganese and verapamil decrease the magnitude of digitalis induced delayed afterdepolarizations[40,41] in addition verapamil counteracts the effects of digitalis on the slope of phase 4 depolarization and automaticity[41] These observations support the view that an inward current carried by calcium ion is responsible at least in part for the changes in diastolic membrane potential that are induced by digitalis Before this thought which would have important implications both mechanistically and therapeutically can be accepted, further identification and verification of the ionic events underlying digitalis effects on phase 4 are required

C Effect of digitalis on conduction Electrophysiologic studies have shown that when phase 4 depolarization decreases the membrane potential at which action potentials are initiated

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ond driven response, however, now is initiated near the peak of the afterdepolarization induced by the premature response and fails to conduct to the myocardium In *D*, the first driven response is similar to the last in *C* and does not propagate However, the premature response occurring at a short coupling interval and a higher level of membrane potential, does conduct to the myocardium This propagated depolarization is followed by another depolarization of the Purkinje fiber, probably due to re entry Although the re entrant depolarization does not propagate back to the myocardium its voltage time course of repolarization is such that the next driven action potential instead of occurring at the peak of an afterdepolarization is initiated at full repolarization The effect of the re entrant depolarization, then has been to facilitate conduction of the next driven depolarization to the myocardium It is apparent from this figure that the interaction between digitalis induced delayed after depolarizations and premature action potentials can result in concealment of conduction within the Purkinje system and in complex disturbances of rhythm including re entry

Digitalis toxicity II Indirect' or autonomic effects of digitalis

Excessive digitalis concentrations may result in an exaggeration of the antiarrhythmic effects attributed to its interactions with the autonomic nervous system Hence, excessive cholinergic and antiadrenergic effects on the sinus and atrio ventricular nodes may result respectively in marked sinus slowing or sinoatrial block and in atrioventricular block It is likely that these con centrations of digitalis are also exerting direct toxic effects on cardiac specialized conducting cells which are similar to those described for Purkinje fibers

In the atrial and ventricular specialized con ducting systems, digitalis and sympathetic stimulation or amines appear to have some facilitative effects For example, both may in crease the slope of phase 4 depolarization and the spontaneous rate of ectopic pacemakers [19 23] There is evidence that intact cardiac sym pathetics and endogenous catecholamine release not only may facilitate toxic effects of digitalis but actually may be necessary for the expression of toxic arrhythmias [44] These observations do not indicate that in the absence of normal sympathetic function enhanced automaticity will not occur as a result of digitalis toxicity, but rather, that the time of onset of ectopic pacemaker function may be delayed and spontaneous rate reduced

Conclusion

We have described the interactions between the autonomic nervous system, the cardiac cell, and digitalis in the hope of clarifying the mechanisms thought responsible for the antiarrhythmic and the toxic effects of digitalis Although much of the information reported was obtained from studies of experimental animals, we have attempted where possible to correlate these observations with clinical events It is of interest that in recent studies digitalis induced delayed afterdepolarizations have been elicited in human atrial tissues (A Spotnitz, personal communication) While this observation is encouraging with respect to the applicability of the data obtained from studies on canine and rabbit hearts, the extent to which delayed afterdepolarizations are responsible for the clinical spectrum of digitalis toxicity in the human must be the subject of considerable further study

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Development and management of extrapyramidal symptoms in hypertensive patients treated with diazoxide

Diazoxide a powerful vasodilator[1] has recently been reintroduced into the long term therapy of severe hypertension because of its effectiveness despite its many side effects [2 3]

The occurrence of renal sodium retention in all the patients and its management by the use of furosemide or ethacrynic acid[4] and the prevention of hyperglycemia by the oral administration of sulphonylur as[3] has been well documented. During four years work with diazoxide which involved the acute and chronic management of 100 severely hypertensive patients [5] the development of extrapyramidal symptoms a diazoxide side effect not previously reported, was observed in 15 per cent of the patients

The symptoms ranged from restlessness which could easily have been diagnosed as func ional, to full blown Parkinsonian syndromes with oculogyrus trismus rigidity and tremor There was a relationship to dosage in that symptoms requiring treatment occurred in patients with a mean serum diazoxide level of 98 8 ± 24 42 mg per liter while patients not requiring treatment for extrapyramidal symptoms had their hypertension stabilized on a mean serum diazoxide level of 55 0 ± 21 55 mg per liter This difference was highly significant

In individual patients the causal relationship between the administration of diazoxide and the appearance of extrapyramidal symptoms could often be established by the occurrence of the syndrome after the introduction of diazoxide when no other drugs were administered which are known to cause this effect and also by its disappearance when the diazoxide dosage could either be diminished or stopped. In one patient (Fig 1) whose progress was followed by daily

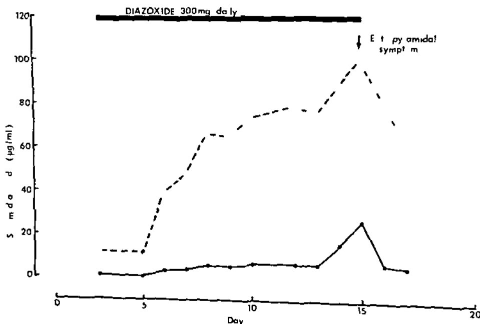


Fig 1 Total serum diazoxide levels (dotted line) and estimated free diazoxide levels (solid line) Free diazoxide level was taken to be 9 per cent of total serum diazoxide with a maximum binding capacity of 16 mg per 5 Gm of albumin per 100 ml[6]

Annotations

Use of multiple-choice questions in testing

Multiple choice questions have become the major instrument of testing in technologic medicine This is partly because medicine pioneered their introduction [1, 2] and partly because medicine s factual content lent itself so easily to exploitation by the method of multiple choice So widespread and so well developed are multiple choice techniques that it has become almost impossible to challenge the system without invoking wrath from those who are now entrenched behind banks of questions and the computer techniques of analysis Yet medicine with its diverse goals of education is a place where slavish reliance on multiple choice should first be questioned

What are the objectives of medical education? They are the inculcation of facts attitudes and skills Only the first can be easily tested by any techniques For the second and third, we are thrown back on the subjective judgments of peers and seniors assessments which are always likely to be conditioned by the desire to produce a next generation in the likeness of the past Thus is preserved a profession which has a long tradition and which clings to its innate conservatism but which at the same time provides just because of this *characteristic an anchor point for the sick patient*

Many exponents of multiple choice techniques have felt it easy to devise questions which require other qualities than simple recall from one s mental data bank of facts learned by rote Unfortunately there is as yet little support for the view that it is possible to test skills such as problem solving or concept formation by multiple choice techniques Work by the author[3] and by Cox[4] *suggests that it is extremely difficult to* arrive at a consensus of what is meant by a question and what level of intellectual skill it is testing When one asks a group of examiners what they *mean* by a question the answers one gets are strange to say the least

One should not despair at these nihilistic results We must realize that our analysis of the educational task is still in its infancy In relation to the goals of medical education multiple choice tests are still crude But " many would say "when it comes to facts I can test these well with a multiple choice technique Not so is the considered reply Facts for one are conjecture for another and Cox and colleagues[5] have again shown that truth is regional and conditioned by educational techniques The factual range is limited by the need for consensus so that contentious facts can rarely be dealt with by multiple choice *Even if we can deal with banality is* it really so important that we impart facts and test them as distinct from dealing with ideas?

The answer to the last question is probably a qualified yes We do need to ensure that there is a core of factual knowledge that our student colleagues (and ourselves) have assimilated. We do need to update that core all the time and methods for this are available which can ride on the vehicle of multiple-choice questions which in turn, are based upon the analysis of factual objectives [6] The danger lies in assuming that this is the be all and end all of testing and evaluation or that *per contra we can formulate* multiple choice tests to analyze other intellectual skills We may in the future be able to do this but our ability to do so will rest on advances in educational research One is reminded of Hudson s[7] early ex*periments which showed that the young solved problems not* so much by intellectual striving but by acquiring the appropriate data and prefabricated concepts. Perhaps this is what happens in medicine and Cox[5] has hinted at this

One other fascinating area which the recent debate on M C Q s has uncovered is what is meant by plain English The response to a deliberately provocative paper[8] was that *because it contained complex statements written with neces*sary parenthetical clauses it was another contribution to incomprehensible educational jargon There exists apparently a school of reductionists grammarians and semanticists (perhaps semiologists in the modern climate) who believe unrelentingly in Wittgenstein s profound but simultaneously trite statement What can be said at all must be said clearly to which I understand Schrödinger was moved to reply When it can t is when it becomes interesting No one would contest that if one can reduce explanation to the simplest words and phrases this is a good thing At the same *time it is necessary to embrace complexity when complex* ideas must be expressed. Education is a complex subject and the failure of some to grapple with the difficult ideas that are attracting a new vocabulary and a new phraseology may tell us more about them than about the subject It is a form of semantic Ludditism to spend more time criticizing the language and expression than the ideas of those who aim for educational innovation Perhaps it indicates an inability to move with the ideas which has always been a characteristic of clinical medicine A maieutic process is required to transform medical education from the casual hobby of the many and the prejudice of some to the *serious study of* all those who presume to teach The midwifery involved will be painful both to those who cannot express themselves without resorting to jargon and those who are convinced that sentences are incomprehensible if they cannot be contained within twenty two syllable words and one conditional clause

All this may seem a far cry from the technical needs of the readers of the JOURNAL However there can be few who are not now involved in the technology of multiple choice questions We must examine this educational tool with the same critical attitude we turn on a scientific endeavor in our *chosen discipline Thus the matter of* education is the concern of all clinicians

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Furthermore he eventually returns home from the hospital anyway and must receive care at home

Why is home care not used more? Because it is inconvenient and more time consuming for the doctor especially considering the tremendous shortage of doctors, and because the public has the impression that good medical care for all illnesses is only possible in a hospital and that complex diagnostic procedures and measurements and therapeutic measures are always necessary for excellent medical care Patients expect to be fed by vein and their families accept this practice as routine The need for greater use of home care of sick people including those with heart disease reflects the need for better doctor patient family and home relationships Hospitals should be used only for those who really cannot be treated properly at home and who really need hospitalization This practice not only would make sick people happier but it would reduce the cost of medical care considerably

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Urokinase in thromboembolic disease Pulmonary embolism

In the continuing search for new and improved methods of treating venous thromboembolism the concept of dissolving clots has always held attraction for investigators in the field Despite the early investigations of streptokinase the inability to produce a purified product which could be safely administered kept its application limited to investigational use

Currently heparin administered intravenously is the drug of choice rapid action predictable response and mechanism of action blocking platelet thrombin interaction are its advantages Its disadvantage is that it is not thrombolytic and therefore cannot directly dissolve clots either in the pulmonary circulation or in the deep veins of the legs where the vast majority of pulmonary emboli originate What dissolution of thromboemboli occurs with heparin therapy is a reflection of natural lysis activated by the thrombolytic process In situations where accelerated lysis of clots is desirable i e in extensive pulmonary embolism with congestive failure or hypotension or in those with previously compromised pulmonary circulation natural thrombolysis appears to be depressed In addition serious hemorrhage may result from heparin therapy For these reasons the search for an "ideal" agent to treat thromboembolism continues

In recent years two thrombolytic agents have undergone extensive basic investigations a purified streptokinase (SK) and the new urokinase (UK) In 1964 the Committee on Thrombolytic Agents of the National Heart and Lung Institute decided to concentrate its efforts on UK the naturally occurring plasminogen activator excreted by the kidney Extensive investigations have shown UK to be identical with the plasminogen activators released from human tissues In its favor is the fact that it is not antigenic being of human origin it is not pyrogenic having been purified sufficiently to remove trace contaminants and its administration does not appear to require precise dosage and complex or cautious laboratory control Its principal disadvantages are temporary prohibitive cost and unavailability for general use

Once early feasibility trials showed that UK was safe and simple to administer a large multicenter trial involving 14 institutions was established to compare the results of UK followed by heparin (H) therapy with the use of H alone The answer sought was a significant difference in the observed rate and extent of clot resolution in the two treatment groups The study randomized and modified double blind in design admitted 160 patients with acute pulmonary embolism proved by perfusion lung scans and selective pulmonary angiograms

Since UK or H was administered by continuous infusion for 12 hours during the "therapeutic" period (now administered for 24 hours) assessments of change were made within 24 hours of the beginning of therapy by control and post therapy pulmonary angiograms hemodynamic measurements and serial lung scans In addition other clinical and laboratory abnormalities due to pulmonary embolism were noted for any differences in rate of change towards normal in the treatment groups This Annotation is based on the official publication of the trial results reported in Circulation [1]

During the two year period of the trial 78 patients received H and 82 received UK followed by H The angiographic assessment of 24 hour change in the UK group showed a significant accelerated resolution of pulmonary embolism in comparison to the H group particularly impressive was the difference in those with massive pulmonary emboli and in the small group with massive emboli and shock Lung scan assessments of change also showed a significant and greater improvement in re perfusion in the UK group than in the H group In the few patients who had massive embolism with shock the reperfusion in the first 24 hour period following UK therapy was striking Similarly the improvement in hemodynamic abnormalities following the embolic episode was significantly greater in the UK group than in the H group These included central venous pressure right ventricular systolic and end diastolic pressure pulmonary arterial mean pressure total pulmonary resistance and arterial oxygen tension

Bleeding complications were high in both groups 27 per cent in the H group and 45 per cent in the UK group It was more frequent in invaded sites—e g catheter cutdowns arterial catheters or punctures particularly in the UK group—but in noninvaded areas no significant difference was noted

serum diazoxide measurements the calculated free diazoxide serum levels showed a sharp peak which coincided with the onset of a severe Parkinsonian syndrome This syndrome resolved with the fall of the free diazoxide level Although most of the hypertensive patients treated with oral diazoxide had some impairment of renal function which may have been a contributory factor to the development of extrapyramidal symptoms because diazoxide accumulates in renal failure (Pohl J E F Thurston H and Swales J D unpublished observations) the syndrome also occurred in patients with normal renal function In particular the patient whose serum diazoxide level was monitored daily (Fig 1) had normal renal function

The reversibility of extrapyramidal symptoms attributed to diazoxide either by the exhibition of standard anti Parkinsonian remedies or in milder cases by the use of diazepam and the complete resolution of this syndrome in those cases when diazoxide dosage could be reduced or stopped must be stressed

The observations are both of clinical and of theoretical relevance Physicians who are prepared to use diazoxide as a long term hypotensive agent require an up to date knowledge of all the side effects likely to be encountered and how they can be managed The fairly common occurrence of extrapyramidal symptoms in a setting of oral long term diazoxide therapy and the ease with which this side effect can be managed therapeutically is important in this context The attribution of Parkinsonian side effects to diazoxide a benzothiadiazine is also theoretically interesting because it suggests a central effect on dopaminergic neurotransmission an action which has not been previously suspected for this chemical class of compounds The occasional occurrence of depression in patients on diazoxide and the clinical impression that this is more common in patients showing extrapyramidal side effects adds further weight to this suggestion

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A need for more care at home

It is unfortunate that cardiologists and other specialists do not encourage visits to and care of patients in their own homes This trend reflects largely the doctor s desire to gather all of his patients in one hospital for his own convenience as well as the impression that hospitalization is necessary for the best medical care The public already has accepted these two reasons as being axiomatic and this is certainly understandable But what about the patient? Few patients enjoy a hospital atmosphere apprehension and expectations of the worst are ever present in the minds of most patients confined to a hospital room The high costs of hospitalization and often impersonal attitude of those in attendance unfortunately even doctors are not conducive to rest and relaxation The hospital routine is already established to meet the needs of the hospital for the average patient and for administrative convenience The average hospital patient could best be treated at home or at the physician s office There is hardly need to list the disturbances and detached activities of a hospital with which the patient must contend for example the changing of bed linens and drinking water at 5 30 A.M sweeping and scrubbing of the floor at 6·00 A M emptying of commodes recording pulse and respiratory rates and temperature at 6 30 A.M changing of nurses at 7 00 A M administration of medicines bathing the patient serving breakfast collecting blood urine and stools and performing various other routine procedures.

The patient at home is not on hospital routine but is on home care planned, established and enforced by those who love him and who have a sincere interest in his welfare comfort and relaxation—and at little extra cost To be cared for by a spouse or other family member with the rest of the family close by in the familiar and comfortable environment of the patient s own home must be extremely beneficial to the patient s health and rate of recovery Furthermore few unnecessary procedures are requested and instituted and since less is done errors are less likely to occur such as receiving another patient s medicine The patient is allowed to rest and sleep to his greatest advantage and is not disturbed because of policies and principles of hospital routine administration and operation With few exceptions he can even receive more and better care directly from his visiting doctor

Letters to the Editor

Phentolamine and acute myocardial infarction

To the Editor

We read with great interest the study of Gould and associates[1] concerning the beneficial effects of phentolamine in patients with acute myocardial infarction The authors felt that this alpha adrenergic blocking agent can improve ventricular performance by the dual mechanism of decrease in the afterload and increase in contractility However it has been shown that a decrease in aortic pressure may increase the magnitude of myocardial ischemia in dogs subjected to transient occlusion of a coronary artery due to reduction of the coronary perfusion pressure[2] The area of ischemic myocardium was estimated by epicardial ST mapping On the contrary studies carried out in hypertensive patients with infarction have shown that decreasing blood pressure with trimethaphan resulted in reduction of the size of the infarct as assessed from the rate of disappearance of serum creatine phosphokinase activity[3] This beneficial effect was attributed to reduction of myocardial oxygen consumption requirements There may well be an optimal level (not yet defined) of pressure for coronary perfusion in man which probably varies among individuals[4] With a pharmacological agent such as phentolamine which possesses both positive inotropic effects (which increase oxygen demand) and alpha adrenergic blocking actions (which by decreasing afterload, decrease oxygen demand but simultaneously affect coronary perfusion in an unpredictable way) it is difficult to delineate clearly the effect on the ischemic myocardium It is interesting that the authors found some increase although small of the tension-time index. Also it is striking that a few patients who were hypotensive in the control state had hemodynamic improvement after phentolamine effusion

It should be kept in mind that measurement of hemodynamics is not enough to characterize fully the performance of the ischemic portion of the ventricle Any change in performance of the ischemic segment could have been masked by changes in the non ischemic areas. Increased inotropy can transiently improve performance at the cost of increasing ischemia The effect of phentolamine on the ischemic ventricle might have been better assessed by using an indicator of the size of the infarct. Precordial ST mapping[5,6] or creatine phosphokinase disappearance curves are such indicators

Precordial ST mapping can be applied serially during control and experimental periods and should probably be used to complement hemodynamic measurements during interventions aimed at reducing the size of myocardial infarction or preventing further extension

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Reply

To the Editor

We can understand the concern about phentolamine s effect on coronary perfusion expressed by Drs Madias and Hood The question they pose is simply Will phentolamine improve the coronary blood flow in patients who have recently sustained an acute myocardial infarction?

We have recently addressed ourselves to this problem Eight patients with a recent myocardial infarction received 10 mg of phentolamine at an infusion rate of 0 3 mg/minute Coronary blood flow was measured before and immediately after the phentolamine infusion using the isotopic method of Donato and associates[1] All of the patients demonstrated a rise in the coronary blood flow after the phentolamine infusion The average pre drug value was 89 3 ± 29 9 ml/minute per 100 Gm myocardium After phentolamine the average myocardial clearance rose to 117 3 ± 33 3 ml/minute per 100 Gm myocardium ($p < 0.01$)[2] Thus the vasodilator phentolamine can not only improve cardiac hemodynamics but can also increase coronary blood flow

We agree that precordial ST mapping and creatine phosphokinase disappearance curves are helpful in assessing the extent of the infarction The effects of phentolamine on these parameters will be of great theoretical and practical interest

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The increased bleeding in both groups was undoubtedly due to the invasive nature of the protocol In patients receiving H the bulk of bleeding occurred when the clotting times were over 60 minutes whereas no patients bled with clotting times less than 30 minutes In contrast once a lytic state was established by UK there was no correlation between degree of lysis and bleeding

No significant difference in mortality rates was anticipated nor was one found Since the over all mortality rate was eight per cent the trial would have required high numbers to show any difference The group II S (hypotension-submassive embolism) patients had the highest mortality rate—100 per cent reflecting the importance of underlying cardiopulmonary disease in influencing outcome Group II M (hypotension-massive embolism) patients showed the next highest mortality rate—18 per cent Eleven patients from several institutions were withheld from the trial because they were considered too sick Pulmonary embolectomy was attempted in all and was successful in four The mortality rate here of 64 per cent might be compared to the group II M mortality rate of 18 per cent following medical therapy but in all likelihood the two groups may not be entirely comparable However there is a strong suggestion that in patients with massive emboli the mortality rate is less with vigorous medical therapy

Despite these impressive results attesting to the superiority of UK over H UK is not available for general clinical use Its prohibitive cost stemming from the cautious handling and purification of enormous amounts of human urine keeps its present application on an investigational basis However newer methods utilizing human kidney tissue cultures have produced a high grade UK which appears to be identical in composition and action to the human urine product Should it withstand further investigations, a source of relatively inexpensive UK will be available In the meantime further investigations are required before the drug is released for general use (1) Is UK more effective and safer than embolectomy in massive pulmonary embolism? (2) Is there reduction in mortality rate from pulmonary embolism with UK therapy? (3) Can bleeding complications be minimized? Preliminary observations from the Phase II trial comparing UK with SK suggests that bleeding complications are minimal when invasive procedures are avoided (4) How effective is thrombolytic therapy in other thromboembolic states e g acute myocardial infarction and cerebral thrombosis?

Although these questions may require some years to answer the release of UK for pulmonary embolism seems a desirable and forseeable step pending completion of investigations into a low cost method of production

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REFERENCE

1 The Urokinase Pulmonary Embolism Trial A National Cooperative Study Circulation XLVII Supplement II 1973

Book reviews

Cardiovascular Disease in the Tropics Edited by A G Shaper M S R Hutt and Z Fejfar London, 1974 British Medical Association, 394 pages

This edited book contains contributions of many clinicians from various parts of the world. This reviewer is impressed with the fact that the book contains a series of papers in which the reader is not readily aware of who is responsible for each report as he studies the material unless he refers back repeatedly to the table of contents Although the book refers to heart disease in the tropics, it is primarily concerned with heart disease in tropical Africa These accumulated papers represent selected aspects of heart disease as related to tropical Africa with emphasis on epidemiology Those who are interested in heart disease in tropical Africa will find much useful information in this book However this is not intended to be a complete discussion of all aspects of heart disease

Physicians and students working in the tropical areas of Africa will find this to be a useful adjunct to their more extensive use of the medical literature books and monographs on cardiology Except for specific diseases such as endomyocardial fibrosis a relatively rare disease the manifestations and management of diseases of the heart are essentially the same throughout the world. The stress of heat associated diseases such as parasitic infections malnutrition and anemia and the social and economic factors which modify the expressions and management of heart disease are different in the tropics The manner in which such factors modify the clinical aspects of heart disease in the tropical areas of Africa needs careful consideration as indicated in this publication These peculiarities of the tropics and of Africa are best learned from actual practice of medicine in tropical Africa Cardiologists as well as students and all physicians will find this to be an interesting informative and useful book

A Practice of Cardiac Catheterisation 2nd Edition By David Mendel London, 1974 Blackwell Scientific Publications 400 pages

This second edition of A Practice of Cardiac Catheterisation will be another success for the book The author and his contributors have brought the first edition up to date Coronary catheterization is emphasized in this edition. Anyone who wishes to learn the technic of catheterization will find this to be an excellent book to study The illustrations are good, the text is clear and the problems associated with the procedure are considered. Cardiac catheterization is increasing in use all the time This renders a book of this clarity and practicability even more useful The book is highly recommended.

Electrocardiography Practical Applications with Vectorial Principles By Edward K Chung Hagerstown Md 1974 Harper & Row 595 pages

This is a standard textbook on electrocardiography Chung has clearly presented the subject He has not attempted to explain in detail the mechanisms for the changes noted in the electrocardiogram in association with cardiac disease states. It is well known that there is a considerable overlap of normal and abnormal manifestations in the electrocardiogram, but it is necessary for the student to indicate this especially when clearly evident However from Figures 3 to 5 on page 31 for example the electrical axis of the normal electrocardiogram is not limited to 0 degrees to +90 degrees orientation in the frontal plane This illustration is misleading because there is considerable overlap of normal and abnormal direction of the QRS axis in the frontal plane Nevertheless this book is well organized the illustrations as a whole are well chosen and the presentation is lucid. This is a good addition to the books on electrocardiography for physicians and students

Clinical Vectorcardiography 2nd ed. By Te Chuan Chou Robert A Helm and Samuel Kaplan New York, 1974 Grune & Stratton, Inc 465 pp

This second edition of a good book on vectorcardiography is welcomed The authors have produced a useful book for beginners in electrocardiography as well as for those who are already seriously involved in the interpretation of vectorcardiograms for clinical practice The book is accurate and lucid The illustrations are clear well selected and numerous The authors very nicely correlate the spatial vectorcardiograms with the electrocardiograms and clinical data In some instances autopsy findings are included. The fifty vectorcardiograms and associated electrocardiograms included in Section 3 of the book provide a good source of material for training in the interpretation of vectorcardiograms It is not always clear to the reader of this book as to the fidelity of the apparatus used to obtain recordings The book is highly recommended for all who interpret electrocardiograms and vectorcardiograms This book is useful to those who even use different lead systems from those employed by the authors.

The Physiological Basis of Starling's Law of the Heart Ciba Foundation Symposium 24 Amersterdam 1974 Elsevier/Exerpta Medica/North Holland, 304 pp $15 40

This book is concerned with the physics and biophysics of myocardial contraction The function of the myosin and actin fibrillae and of other organelle concerned with myocardial contraction are presented, indicating anatomic and functional relationships Since the preparations usually studied ultrastructurally and physiologically are so different from that which must exist in an intact mammalian heart the quantitative evaluations described in this book must be considered cautiously The force–velocity length–time course curves are interesting but also likewise represent data from rather artificial myocardial preparations The presentations are interesting and should provoke thought among readers involved in studying cardiac contraction and relaxation As usual the discussions are of considerable value to readers who were not present at the conference The subject is important and the book is a good one

Cardiac Arrest and Resuscitation Fourth edition Edited by Hugh E Stephenson Jr Saint Louis 1974 The C V Mosby Company 998 pp $45 50

Stephenson has edited a good and successful book on cardiac arrest and resuscitation. The book is authoritative and comprehensive It is well planned and supported by excellent

Ambulatory ECG recording

To the Editor

I enjoyed the article by Dr Israel M Stein in your July 1974 issue entitled Ambulatory long term electrocardiography—the LCG (AM HEART J 88 37 1974) From this brief literature review it is apparent that Dr Stein has joined a distinguished and rapidly increasing list of investigators and clinicians who have discovered the wide spectrum of uses of ambulatory ECG recording I applaud his enthusiasm for the technique However I feel strongly that his newly coined reference to the technique as LCG is both unnecessary and confusing

Since the introduction by Norman J Holter in 1957 of a diagnostic technique for continuously recording an ambulatory patient s electrocardiogram with subsequent high speed analysis of the resulting recording a variety of terminology has been used in the literature to describe the procedure Depending on the time and geographic location papers have referred to the technique as radiocardiography radiotelecardiography storage telemetry long term continuous electrocardiography dynamic electrocardiography Holter electrocardiography Holter monitoring and Holter recording I submit that by far the most commonly used names for the procedure are Holter ECG and Holter recording These would seem to be the most appropriate generic names regardless of the specific apparatus employed This is particularly relevant since some of the other terminologies have been embraced by particular instrument manufacturers By adopting the term Holter ECG we also preserve a tradition in science by honoring the inventor of the technique

It should also be pointed out that Dr Stein footnotes his comment that several devices are available commercially with the names of three equipment sources Avionics Medcraft and Dr Stein s own Clinical Data Services (Helega recorder) In fact there are at least three other manufacturers of recording equipment for Holter electrocardiography which include Oxford Instruments Annapolis Md Siemens Erlangen West Germany and Cardio Dynamics Laboratories Inc Beverly Hills Calif

Joseph J Sheppard Ph.D President
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REFERENCE

1 Holter N J Radioelectrocardiography A new technique for cardiovascular studies N Y Acad Sci 65 913 1957

Reply

To the Editor

I wish to thank Dr Sheppard for his comments I agree with Dr Sheppard that a variety of terminology has been used in the literature to describe this procedure and that no generic term has been formally adopted Current trends do not favor the use of eponyms as will be noted in several editorials recently published A much more favorable approach is the use of descriptive terminology Therefore I suggest that the expression long term ECG be used to identify this technique It is perhaps of further interest that the original patent describing the long term ECG procedure bears the names of the two co inventors Holter and Glasscock

With respect to the delineation of the manufacturers of available equipment for the performance of the long term ECG the listing in the article was by no means meant to be a complete one Indeed several other devices are available aside from the additional ones mentioned by Dr Sheppard in his letter Parenthetically the tape recorder used by Clinical Data is made to our exclusive specifications by a Swedish manufacturer and is not derived from the Helige Company

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3 Cross H E. The use and abuse of eponyms, Am J Ophthalmol 76 598 1973
4 Holter N J and Glasscock W R Electrocardio recording and reproducing system U.S Patent 3 229 687 Jan 18 1966

Ventricular function curves

To the Editor

In a recent article entitled Ventricular function curves from the cardiac response to angiographic contrast A sensitive detector of ventricular dysfunction in coronary artery disease (Brundage and Cheitlin AM HEART J 88 281 1974) there seems to be some confusion in the usage of the terms compliance and stiffness" of the left ventricle Under *Methods* the authors defined compliance as $\Delta P/\Delta V$ which in fact represents stiffness Compliance is the reciprocal of stiffness Under *Results* the authors described a significant decrease in compliance after angiogram in Group B which was however depicted in Table I as an increase in $\Delta P/\Delta V$ from the pre angiogram value of 0 29 to 0 42 after angiogram

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Reply

To the Editor

Dr Cheng is quite correct in his definitions of "compliance and stiffness " We should have defined $\Delta P/\Delta V$ as stiffness and not compliance in our methods However in our discussion of the results we were consistent in implying that ventricles with coronary artery disease were more stiff—i e less compliant than normal ventricles both before and after angiogram This was represented by higher values of $\Delta P/\Delta V$ in Table I for the ventricles with coronary artery disease

The terms compliance and stiffness are analogous to the vintner describing a wine as more dry or less sweet "

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Books received

Epidemiology—An Introductory Text By Judith S Mausner M D M P H and Anita K Bahn Sc D M D Philadelphia 1974 W B Saunders Company 362 pages

The Alimentary Tract By Harvey J Dworken M D Philadelphia 1974 W B Saunders Company 384 pages

Kardiologie Hypertonie By Von F Anschuta U Gaissmaier W Hann D Klaus H Lydtin, J Schmidt and E Zeh Berlin, 1974 Springer Verlag 242 pages Price $9 30

Einfuhrung in Die Vektorelektrokardiographie By Dr Med. U Thomae Stuttgart 1974 F K Schattauer Verlag 96 pages.

Physiology and Biophysics II Circulation Respiration and Fluid Balance 20th edition Howell Fulton Textbook of Physiology and Biophysics Edited by Theodore C Ruch Ph.D and Harry D Patton, Ph D M D Philadelphia 1974 W B Saunders Company 546 pages

illustrations The discussions are concerned with practically all aspects of cardiac arrest and resuscitation As would be expected, the book describes technic indications for expecting an arrest prevention medical and surgical management of the patient during the crisis period and afterward action and use of drugs incidence and other aspects This is an excellent and valuable book which should be carefully studied by all physicians who manage cardiac disease and certainly by those who work in a coronary care unit

Shock in Myocardial Infarction Edited by Rolf M Gunnar M D Henry S Loeb M D and Shahbudin H Rahimtoola M B New York and London 1974 Grune & Stratton Inc 295 pages

This edition of the clinical cardiology monographs on cardiogenic shock following myocardial infarction reviews this important problem thoroughly The editors of the book include many contributors who review some of the fundamental concepts concerned with the production of shock and principles in management The hemodynamic disturbances associated with shock left ventricular function monitoring arrhythmias associated with shock medical and surgical treatment are among the subjects presented. Each chapter is supplemented with a bibliography This review of this important subject is welcomed and is a good one Students and physicians as well as nurses who work in the coronary care units will find the book to be useful and worth studying

American Heart Journal

April 1975 Volume 89 Number 4

Editorial

What is the role of pulmonary embolectomy?

Arthur C Beall Jr M D
John J Collins Jr M D
Houston, Texas and Boston, Mass

On page 413 of this issue appears an article entitled Treatment of massive pulmonary embolism The role of pulmonary embolectomy [1] There can be no doubt that the question of the role of pulmonary embolectomy is one in which answers are sorely needed Unfortunately the article by Alpert and associates does not provide all the answers despite careful analysis of a large group of patients with massive pulmonary embolism

It would appear that failure of this article to answer some of the questions it sets out to explore relates in part to the selection of patient population for analysis The group selected consists of 45 patients with massive pulmonary embolism (occlusion of more than 50 per cent of the pulmonary circulation) from among 145 patients with pulmonary embolism documented by pulmonary angiograms performed on 544 patients during a 10 year period at the Peter Bent Brigham Hospital From this analysis the article concludes that in this selected group in none of the patients with massive pulmonary embolism with shock who died was pulmonary embolectomy both feasible *and* clinically appropriate [1]

While this may be the case in this selected group of patients the potential role of pulmonary embolectomy remains far from clear A more revealing approach to this question would have been an analysis of the 310 patients dying at the Peter Bent Brigham Hospital during this same 10 year period in whom pulmonary embolism was listed as a primary diagnosis Perhaps the authors did not select such an approach because of their assumption that The very patients in whom embolectomy would be life saving are those who die within minutes of the embolic episode However since they die before the diagnosis can be established embolectomy is obviously not possible [1] This assumption similar to that of Gifford and Groves[2] which is quoted in the article is based upon the concept that a patient with acute massive pulmonary embolism must live for at least an hour after definitive diagnosis by pulmonary angiography for the pump team to be mobilized in order for pulmonary embolectomy to be technically feasible Thus we see a failure to recognize the possibilities inherent in a multidisciplinary team approach to the patient with acute massive pulmonary embolism

The potential of such a team approach recently was demonstrated in one of our hospitals [3] In this hospital patients suspected of sustaining acute massive pulmonary embolism are seen immediately and simultaneously by both the Cardiology Service and the Surgical Service If the patient has sustained cardiac arrest and is requiring cardiopulmonary resuscitation or if it is

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Course in cardiology

A three day review of recent advances in coronary heart disease will be held at the Balboa Bay Club Newport Beach California March 27 through March 29 1975 under the sponsorship of the University of California Irvine School of Medicine and the Pasadena Cardiovascular Research Foundation For further information please write John A Udall M D 101 City Drive South Orange Calif 92668

Workshop on contractile behavior of the heart

The third international workshop on contractile behavior of the heart will be held on September 4 and 5 1975 in Antwerp Belgium The theme of the workshop will be 'The Heart Muscle and Pump The workshop will be given under the auspices of the University of Antwerp and will be under the direction of Drs D L Brutsaert and F L Meijler

For further information please contact Dr Dirk L Brutsaert Professor of Physiology University of Antwerp Groenenborgerlaan 171 2020 Antwerp Belgium

Workshop in echocardiography

A workshop in echocardiography will be held at the Thoraxcenter Rotterdam The Netherlands on September 4 and 5 1975 The program will cover the theory and current state of ultrasonic techniques with emphasis on clinical applications Instructions in echocardiographic interpretation will be given

For further information please write J Roelandt, M D Thoraxcenter P O Box 1738 Rotterdam The Netherlands.

Clinical communications

Treatment of massive pulmonary embolism the role of pulmonary embolectomy

Joseph S Alpert, M D
Roger E Smith M D
Ira S Ockene M D
Joseph Askenazi M D
Lewis Dexter M D
James E Dalen M D
Boston, Mass

The treatment available for acute pulmonary embolism falls into two different categories prophylactic and definitive Prophylactic therapy focuses on preventing further episodes of pulmonary embolism The emboli already in the pulmonary circulation are not treated per se with the expectation that in vivo fibrinolysis will dissolve them Anticoagulation and venous interruption are the two forms of prophylactic therapy that are in current use

Definitive therapy is directed against emboli already lodged in the pulmonary vascular bed. The aim of this form of treatment is the removal of clots from the pulmonary circulation Pulmonary embolectomy and fibrinolytic agents are the two forms of definitive therapy that have been used

The treatment of choice for submassive (occlusion of less than 50 per cent of the pulmonary circulation) pulmonary embolism is prophylactic—that is anticoagulation and/or venous interruption However the therapy of choice for *massive* embolism—that is when more than 50 per cent of pulmonary circulation is obstructed—is controversial

Many have argued[1-5] that patients with massive pulmonary embolism require definitive therapy specifically embolectomy since such patients have little chance for survival without operation[5] However many other reports have documented that patients with massive embolism survive and that the in situ pulmonary emboli completely lyse with prophylactic therapy alone[6-9]

Since none of these reports were based on randomized clinical trials their conflicting results very likely reflect differences in patient population

Pulmonary embolectomy is a formidable procedure that carries a mortality of 40 to 60 per cent[4,6,10-12] therefore its role in the treatment of patients with massive pulmonary embolism clearly needs definition

We have reviewed our experience with all patients in whom massive pulmonary embolism was documented at the Peter Bent Brigham Hospital

Table I Hemodynamic findings in 45 patients with massive pulmonary embolism (greater than 50 per cent obstruction of pulmonary circulation)

	No of patients	*Per cent of group*
Right ventricular failure (P A mean pressure > 7 mm Hg)	28	62
Hypotension	19	42
Transient no treatment	3	7
Treatment required	12	27
Cardiac arrest	4	9
Hypotension and right ventricular failure	16	36

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apparent that such probably will occur before or during pulmonary angiography, partial cardiopulmonary bypass is instituted immediately by cannulating the femoral vein and artery This is made possible by maintaining a portable pump oxygenator set up at all times which can be primed with 5 per cent dextrose in distilled water by a member of the resident staff while the femoral artery and vein are being cannulated The pump oxygenator then is run by a member of the resident staff until one of the regular extracorporeal perfusion technologists arrives At most this is necessary for only a few minutes, however, since the technologist is notified as soon as the Surgical Service is informed of the case

Once support has been provided by partial cardiopulmonary bypass, the patient is moved to the Radiology Department for definitive diagnosis by pulmonary angiography and subsequently to the Operating Room, where partial is converted to total cardiopulmonary bypass and pulmonary embolectomy is performed Among 17 patients undergoing pulmonary embolectomy in this hospital during a recent 5 year period 11 survived. Of particular significance was the fact that 5 of the 6 deaths resulted from hypoxia in patients in whom partial cardiopulmonary bypass was not used for support, either before availability of the portable pump oxygenator or because its use was not considered indicated Additionally 7 out of 9 patients in whom partial cardiopulmonary bypass was used for resuscitation survived following pulmonary embolectomy, despite the fact that pulmonary embolism presented with cardiac arrest in 7 of these patients

Thus, it would seem that although the role of pulmonary embolectomy in the treatment of massive pulmonary embolism remains to be defined clearly, certain patients can be saved by its use It is also apparent that unless a multidisciplinary team approach is taken to patients with acute massive pulmonary embolism, a number of these patients will die prior to definitive diagnosis by pulmonary angiography and will not be included in analyses such as that of Alpert and associates [1] Selection of patients who survive without assistance until angiography can be performed is similar to the approach of physicians of almost 5 000 years ago as described in the Smith papyrus,[4] whereby the physician only selects for treatment those patients who will probably live and leaves to a Greater Being responsibility for those who will probably die

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2 Gifford, R W and Groves L K Limitations in the feasibility of pulmonary embolectomy Circulation 39 523 1969
3 Ruel G J Jr and Beall A C Jr Emergency pulmonary embolectomy for massive pulmonary embolism Circulation (In press)
4 Breasted J H The Edwin Smith Papyrus Chicago 1930 The University of Chicago Press, Vol I

Treatment	? Embolectomy	
	Clinically appropriate	Technically feasible
Heparin, embolectomy	Yes	No
Heparin	Yes	No
Heparin, IVC tie	No	Yes
Heparin, IVC clip	No	Yes
Heparin, urokinase femoral vein ligation	No	Yes
Heparin, femoral vein ligation	No	Yes
Heparin, attempted IVC clip embolectomy	Yes	Yes
Heparin femoral vein ligation	No	Yes

cal evidence of heart disease at the time of pulmonary embolism. Of fifteen patients who had prior heart disease six had clinical evidence of congestive heart failure before their episode of pulmonary embolism

Massive pulmonary embolism caused severe hemodynamic abnormalities in most of these patients (Table I) Right ventricular failure as judged by a right atrial mean pressure greater than 7 mm Hg developed in 28 of the 45 (62 per cent) patients and hypotension developed in 19 patients (42 per cent) Hypotension was persistent and required vasopressor therapy in 16 (36 per cent) of the 45 patients including four patients who suffered cardiac arrest at the time of the acute episode of pulmonary embolism All 16 of these patients had right ventricular failure

A rigid, universal therapeutic program was not employed during the ten year period covered by this review Therapy in each case was determined by the attending physician However certain therapeutic principles were followed by all the physicians involved Heparin by the intravenous route was administered to every patient unless there were urgent contraindications Heparin dosage varied from 7 500 to 15 000 units every four to six hours Inferior vena caval interruption was elected if there was a contraindication to anticoagulation if there was no evidence of a reversible predisposition to venous thromboembolism or if acute cor pulmonale was present [12] Femoral vein ligation was elected in a few patients who had a contraindication to anticoagulation and were judged to be inappropriate candidates for general anesthesia because of chronic terminal congestive heart failure

The majority of the patients (32 out of 45) were treated with inferior vena caval interruption [12] although a significant number (7 out of 45) of patients received anticoagulants only Three patients were treated with femoral vein ligation and three were treated with pulmonary embolectomy

Results

Hospital mortality in patients with massive pulmonary embolism Ten of the 45 patients with massive embolism died during hospitalization Two deaths were unrelated to pulmonary embolism Both these patients died of acute myocardial infarction with congestive failure These two deaths occurred three and six weeks after acute pulmonary embolism had been documented Both patients had postmortem examinations which showed only minimal residual pulmonary embolism

Thus there were eight deaths related to pulmonary embolism in these 45 patients (mortality equals 18 per cent)

In four of these eight deaths pulmonary embolism was the primary cause of death That is in each of these four patients death was solely due to the effects of massive pulmonary embolism In four other cases pulmonary embolism was a major contributor to death Each of the latter four patients had one or more co existing lethal diseases (Table II) such that pulmonary embolism was judged to have been contributory but not primary in their deaths

In hospital mortality was clearly affected by the occurrence of hypotension with the acute episode of pulmonary embolism Six deaths occurred among the 19 patients (32 per cent) with massive embolism who had any evidence of hypotension In three of these cases pulmonary em

Table II Death from pulmonary embolism primary or contributing 1964 1973 patients with greater than 50 per cent occlusion of pulmonary vascular bed

Patient	*Age*	*Per cent obstruction*	*Type of hypotension*	*Acute RV failure*	*Prior heart disease*	*CHF*	*Other medical problems*	*Time angio to death*
Patients with hypotension								
PF	69	> 75%	Persistent	Yes	Cor pulmonale	No	Severe COPD with cor pulmonale	30 minutes
PS	77	> 75%	Transient	Yes	None	No	Adenocarcinoma of rectum s/p excision 10 days earlier	60 minutes
ST	22	50 75%	Persistent	Yes	None	No	Severe anoxic brain damage 2° to cardiac arrest	48 hours
JS	68	> 75%	Transient	No	Cor pulmonale	No	Recent CVA COPD glioblastoma found at postmortem	8 days
CG	62	50 75%	Transient	Yes	None	No	Metastatic melanoma to brain	4 days
TM	69	50 75%	Persistent	No	CAD acute myocardial infarction	No	Cirrhosis with ascites renal failure	10 days
Patients without hypotension								
AM	60	> 75%	None	Yes	CAD	No	None	6 hours
BS	46	50 75%	None	Yes	Mitral regurgitation aortic regurgitation	Yes	SBE severe CHF	10 days

in the ten year period from 1964 through 1973 Each of these patients was studied by cardiac catheterization and pulmonary angiography The clinical and hemodynamic status of each of these patients was assessed and compared to the results of therapy We have specifically attempted to determine how often pulmonary embolectomy was indicated and equally important how often it would have been clinically appropriate and technically feasible during this ten year period

Materials and methods

Pulmonary angiography has been used to diagnose pulmonary embolism in our laboratory since 1964[13] Our policy has been to perform pulmonary angiography in all patients suspected of having pulmonary embolism Since this philosophy is shared by most physicians at our hospital pulmonay angiography is performed on nearly every patient in whom the diagnosis is seriously considered Angiography is performed even in critically ill patients, including those who are hypotensive and require vasopressors and in patients receiving assisted ventilation

In the ten year period from 1964 through 1973 544 pulmonary angiograms were performed and 144 patients were documented as having acute pulmonary embolism Of these 144 patients 45 had massive embolism that is, occlusion of more than 50 per cent of the pulmonary circulation The angiograms hemodynamic measurements obtained at the time of right heart catheterization and the hospital course of each of these 45 patients were reviewed Follow up information concerning clinical status as of Dec 1 1973 was also obtained for these patients Most patients were re evaluated and examined by one of us In a few instances the follow up information was supplied by the patient's private physician

Patient population The 45 patients with massive pulmonary embolism ranged in age from 17 to 84 years with the majority being older than 50 years (average 57 years) Most of these patients (30 out of 45 67 per cent) were free of clini

with hypotension and 10 out of 12 (83 per cent) patients with right ventricular failure and hypotension survived after vena caval interruption and/or anticoagulant therapy. This is the group of patients in whom pulmonary embolectomy is most frequently advocated.

Late follow up At follow up six months to ten years after discharge from the hospital 29 of the 35 patients who left the hospital were alive and well. Six patients had died: three of myocardial infarction, one of brain tumor, one of pneumonia and dehydration, and one of chronic cor pulmonale secondary to unresolved pulmonary embolism. This latter patient had multiple episodes of untreated pulmonary embolism prior to the episode that brought him to our attention. Three of the patients who died after discharge had postmortem examination. None had evidence of unresolved emboli in the pulmonary vascular bed. Of the 29 patients who were alive at follow up, none had evidence of chronic cor pulmonale by history, physical examination, electrocardiogram, or chest x ray.

Table IV Results of prophylactic treatment* in 39 patients with massive pulmonary embolism according to clinical features

	No of patients treated	*No of patients surviving*	%
Right ventricular failure	23	20	87
Hypotension	15	12	80
Cardiac arrest	2	2	100
Right ventricular failure and hypotension	12	10	83
Prior heart disease	11	8	73

*IVC interruption and/or anticoagulation (excludes three patients with terminal heart disease treated with femoral vein ligation)

Table V Mortality from emergency pulmonary embolectomy

Report	*No of cases*	*Mortality (%)*
Sautter (1965)[8]	12	75
Berger (1968)[3]	7	29
Paneth (1967)[4]	12	67
Cooley (1968)[5]	11	64

Discussion

Pulmonary embolectomy has often been suggested as the therapy of choice for massive pulmonary embolism with hemodynamic compromise.[1-5] There are two potential rationales for pulmonary embolectomy: to increase the probability of survival and to prevent the development of chronic cor pulmonale due to unresolved pulmonary embolism.

Our data have obvious implications as to the first indication of embolectomy, that is, to increase the probability of survival of patients with acute massive pulmonary embolism. The risks of embolectomy must be compared to the probability of survival without embolectomy. As shown in Table V, the majority of patients who undergo embolectomy do not survive. With one exception[3] the reported mortality for emergency pulmonary embolectomy is in the range of 60 to 70 per cent.[10] This mortality must be compared to the mortality of comparable patients with massive pulmonary embolism who are treated with prophylactic therapy as in our series.

The mortality in 26 patients with massive embolism without hypotension in our series was low, 8 per cent. This is much lower than the mortality attendant to pulmonary embolectomy.[4-8,10,12] This indicates that massive pulmonary embolism per se is not an indication for pulmonary embolectomy.

The only group in which emergency embolectomy might be considered in order to increase acute survival is the group with massive pulmonary embolism complicated by hypotension. Of 19 such patients in our series, six died (mortality 32 per cent). However, when we looked critically at the circumstances of the death of these six patients, there was no evidence that embolectomy could have altered their course. Two of these six deaths occurred within one hour of diagnosis and thus embolectomy was not technically feasible. In each of the four patients in whom embolectomy was technically feasible, associated diseases such as metastatic cancer made embolectomy clinically inappropriate.

Thus our data indicate that in patients who live long enough to have pulmonary embolism diagnosed, embolectomy is rarely indicated, technically feasible *and* clinically appropriate. The very patients in whom embolectomy would be life saving are those who die within minutes of the embolic episode. However, since they die before the diagnosis can be established, embolectomy is obviously not possible.

Other investigators have reported a similar

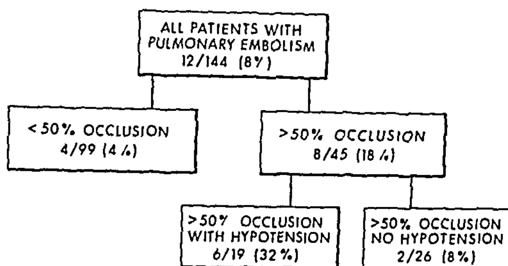


Fig 1 Mortality in acute pulmonary embolism according to per cent obstruction and hemodynamic status

Table III Results of therapy in 45 patients with massive pulmonary embolism (> 50 per cent obstruction of pulmonary vasculature)

Therapy	*No of patients*	*No of deaths due to pulmonary embolism*	*No. of deaths due to other causes*	*No. discharged*	*No alive and well at follow up*
IVC interruption	32	2	1	29 (91%)	23 (72%)
Femoral vein ligation	3	2	1	0 (0%)	0 (0%)
Anticoagulation	7	2	0	5 (71%)	5 (71%)
Embolectomy	3	2	0	1 (33%)	1 (33%)
Total	45	8 (18%)	2 (4%)	35 (78%)	29 (64%)

Ligation or clip of the inferior vena cava

bolism was the primary cause of death In the 26 patients with massive embolism who did not have hypotension there were only two deaths (mortality equals 8 per cent)

The patients with massive embolism and hypotension (mortality equals 32 per cent) are the group in whom embolectomy has been most often suggested Therefore we examined each of the six deaths in this group of patients to determine, in retrospect if pulmonary embolectomy might have been technically feasible and clinically appropriate As shown in Table II embolectomy would have been technically feasible in four of these six patients in that they survived for more than an hour after angiographic documentation of the diagnosis In the other two patients pulmonary embolectomy was not technically feasible in that they succumbed before the 'pump team could be mobilized However pulmonary embolectomy was clinically inappropriate in each of the four patients in whom it was technically feasible because of associated medical conditions One patient had known metastatic melanoma, another had end stage cirrhosis with ascites and renal failure a third had a recent massive cerebrovascular accident and the fourth had suffered severe anoxic brain destruction from a cardiac arrest at the time of her pulmonary embolism All clinicians involved in the care of these four patients agreed that embolectomy was inappropriate Thus in none of the patients with massive pulmonary embolism with shock who died was pulmonary embolectomy both feasible *and* clinically appropriate

Survival in patients with massive embolism Of the 35 patients who survived massive pulmonary embolism, all but one were treated with prophylactic therapy Survival after each of the four forms of treatment is summarized in Table III Patients receiving vena caval interruption had the highest rate of survival

Survival was also assessed according to each patient s clinical status (Table IV) It is of special interest that 12 out of 15 (80 per cent) patients

Left axis deviation: etiologic factors in one hundred patients

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Left axis deviation (LAD) is a common electrocardiographic abnormality whose implications regarding the existence of heart disease has long been of interest. Even if marked, LAD is not correlated with a leftward orientation of the anatomic long axis of the left ventricle, indicating that LAD is primarily related to electrophysiologic properties of the myocardium. Orientation of the electrical axis was once considered useful for detecting left ventricular hypertrophy (LVH) but has proved to be of limited value among the diagnostic criteria which evolved following the introduction of unipolar chest leads. In 1956 Grant[1] reported a high prevalence at autopsy of myocardial lesions, including LVH, in subjects demonstrating LAD beyond −15 in the frontal plane, thereby renewing interest in LAD as an indication of heart disease. An electrocardiographic anatomic correlation by Corne and co-workers[2] in 1956 revealed that LAD beyond −30 was associated with a high incidence of myocardial fibrosis. LVH did not appear to be independently correlated with LAD.[2]

Experimental laceration of the left anterior aspect of the interventricular septum in the baboon produced marked LAD, leading Watt, Murao, and Pruitt[3] to conclude that interruption of the anterior division of the left bundle branch delayed excitation of the anterior left ventricular wall, thereby producing a left superior rotation of the electrical axis. Subsequently, a clinical study by Pryor and Blount[4] concluded that 80 per cent of patients with "true" LAD had ischemic heart disease. In 84 per cent of electrocardiograms with LAD the clinical interpretation implicated block in the left anterior superior fascicle, and if the LAD was beyond −30, such block was implicated in nearly all cases. Most of the related myocardial lesions were infarction or fibrosis.[5]

Various cardiomyopathic states have been associated with LAD due to left anterosuperior fascicular block, such as the familial and the alcoholic varieties, those associated with myotonia atrophica, progressive muscular dystrophy, and Friedreich's ataxia, and the idiopathic myocardial hypertrophies. Systemic diseases capable of involving the conduction system and producing LAD include the collagen vascular processes in scleroderma and lupus and the infiltrative processes of amyloidosis and hemochromatosis. LAD due to congenital heart disease affecting the course of the anterior superior fascicle is a hallmark of endocardial cushion defects, most notably ostium primum atrial septal defect, but also approximately 10 per cent of ventricular septal defects and various malformations of the atrio-ventricular canal. Also, LAD is commonly observed in tricuspid atresia and in some 30 per cent of patients with single ventricle. Surgical injury to the left anterior superior fascicle may occur during procedures in the vicinity of the high ventricular septum, such as relief of congenital subaortic stenosis.

Pulmonary embolism has been identified as a cause of leftward rotation and LAD, which was twice as frequent as RAD but often regressed with time.[6] Another reversible cause of LAD is hyperkalemia.[5]

The significance of LAD as an index of cardiac abnormality has been sought in studies of large populations. Blackburn and co-workers[7,8] have suggested that LAD in a general population may

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paucity of patients in whom embolectomy might have altered the course Gifford and Groves[14] found only five patients who were candidates for embolectomy out of 101 individuals dying of massive pulmonary embolism during an eleven year period at the Cleveland Clinic [14] Myerowitz[15] reported similar findings during a ten year period of time at the Hammersmith Hospital [15]

Thus most patients who die of documented massive pulmonary embolism die too rapidly to mobilize the 'pump team," or have other cardiac or medical diseases that make pulmonary embolectomy clinically inappropriate

Since embolectomy is rarely technically feasible *and* clinically appropriate, the question then arises 'are there other treatment modalities which offer the patient with massive pulmonary embolism a reasonable chance of survival' ? The answer to this question can be found in Tables III and IV, and is clearly yes As demonstrated *above critically ill patients with both right ventricular failure* and hypotension almost always survive if further episodes of pulmonary embolism are prevented by vena caval interruption or anticoagulation

The second potential rationale for pulmonary embolectomy, prevention of chronic cor pulmonale, is equally tenuous Follow up studies have demonstrated that lysis of in situ pulmonary embolism is the overwhelming rule [7 9 16 17] Our previous studies have indicated that chronic cor pulmonale is an extremely uncommon complication of pulmonary embolism in patients who receive appropriate prophylactic therapy [18]

The conclusions seem clear If patients with massive pulmonary embolism and hemodynamic embarrassment receive prophylactic therapy (be it medical or surgical), such that further episodes of embolism are prevented, they will survive and the in situ pulmonary emboli will lyse Lysis of the emboli results in regression of the hemodynamic abnormalities[17] and permits long term survival [18]

Pulmonary embolectomy is certainly not the treatment of choice for patients with massive pulmonary embolism who survive long enough for the diagnosis to be suspected and documented This procedure should be reserved for the exceptional circumstance of persistent hypotension in a patient with documented massive pulmonary embolism whose overall status is such that *pulmonary embolectomy is clinically* appropriate

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Table III Age corrected distribution of LAD

Age	100 Patients (per cent)			Per cent controls	Ratio
	Male	Female	Total		
0 20	1	0	1	2	0 5
21 40	2	0	2	15	0 13
41 50	3	3	6	8	0 75
51 60	9	6	15	16	0 94
61 70	16	11	27	19	1 4
71 80	9	11	20	24	0 83
81 90	14	12	26	13	2 0
91 100	1	2	3	3	1 0

Age	Per cent patients	Per cent controls	Ratio
0-40	3	17	0 18
41 60	21	24	0 88
61 80	47	43	1 1
81 100	29	16	1 8

agnosis was 11 per cent but is probably reduced further by the criteria we have employed.

The regional criteria for infarction were as follows *septal infarction* diagnostic Q wave in Leads V_1 V_2, invariably seen as a QS deflection *Antero septal infarction* diagnostic Q wave in Leads V_1 V_2 V_3 V_4 or failure or r wave pro gression particularly if amplitude diminishes *Lateral wall infarction* diagnostic Q wave in Leads I and aV_L or Leads I and V_6 *Inferior wall infarction* diagnostic Q wave in Leads III and aV_F. Here it should be noted that when inferior infarction produces LAD the Q wave in Lead aV_F must necessarily be large since the net QRS area is negative

LVH was diagnosed when the point score was five or more according to the following system of values summed amplitude of the s wave in Lead V_1 and r wave in Lead V_5 greater than 35 mm (3 points) LAD greater than −15 (2 points) dura tion of QRS 0 09 to 0 10 second (1 point) intrin cicoid deflection in Leads V_5 or V_6 0 04 second or greater (1 point) sloping ST segment displace ment opposite in direction to major QRS deflec tion in the absence of digitalis (3 points) and with digitalis (1 point)

Left anterior hemiblock (LAHB) required a QRS axis at −30 or beyond r wave in Leads III and aV_F which was small and broad (q wave in Lead aV_L is reciprocal finding and generally less striking) *and* an s wave in Lead V_6 which was deep and/or wide Though not required for the di agnosis of LAHB additional features generally present and judged supportive were absence of the septal q wave in Lead V_6 generous amplitude of the r wave in Lead aV_L and s wave in Lead III and a QRS duration of 0 09 to 0 10 second in any of the twelve standard leads [12]

Left bundle branch block (LBBB) and right bundle branch block (RBBB) respectively were diagnosed from common criteria based upon in creased duration of QRS and the direction of forces during the terminal 0 04 second of the QRS interval

Results

Clinical diagnosis The clinical diagnoses in this series of 100 patients with LAD appear in Table II Specifically listed are those diagnoses con sidered relevant to cardiac disease or whose asso ciation with ECG findings may be of interest The miscellaneous category included disorders of the gastrointestinal tract nervous system integu ment, certain infections, exposure to toxic sub stances and neoplasms without cardiac metasta ses

Overt arteriosclerotic heart disease was the most frequent primary diagnosis encompassing 32 per cent of patients In an additional 16 per cent of patients, some degree of coronary athero sclerosis may be suspected from their primary di agnosis which was hypertension in 6 per cent diabetes mellitus in 3 per cent and cerebrovascu lar accident without present hypertension in 7 per cent of the series

The second largest diagnostic category was chronic pulmonary disease of the obstructive emphysematous type representing 11 per cent of the series Also of interest in that 7 per cent of the instances of LAD were observed in asymp

Table I ECG features analyzed in 100 cases of LAD

PR interval
QRS axis
QRS rotation
clockwise
counter clockwise
QRS duration
Infarction
Septal
Anterior
Lateral
Inferior
Left ventricular hypertrophy
Inter ventricular conduction delay
Right bundle branch block
Left bundle branch block
Left anterior hemiblock

Table II Clinical diagnoses in 100 patients with LAD

Diagnosis	Degree of LAD		Total
	0 to −29	−30 to −90	
Arteriosclerotic heart disease	9	23	32
Chronic lung disease	5	6	11
Cerebrovascular disease	0	7	7
Hypertensive vascular disease	1	5	6
Diabetes mellitus	0	3	3
Alcoholism	3	0	3
Dehydration	0	3	3
Rheumatic heart disease	1	1	2
Pulmonary embolism	1	0	1
Cardiomyopathy	0	1	1
Hepatic cirrhosis	1	0	1
Functional psychiatric disorder	2	1	3
Routine electrocardiogram	3	4	7
Noncardiac chest pain	2	1	3
Miscellaneous	11	6	17
Total	39	61	100

be a benign concomitant of aging rather than an indicator of heart disease However, if degeneration of cardiac structures and/or function does accompany aging, is this to be considered normal? Evidently, the semantic question needs to be resolved

An epidemiologic study by Ostrander[9] reported that 41 per cent of persons with LAD beyond −30° were free of overt or clinical heart disease

Isolated LAD appeared to be a common electrocardiographic finding, and over a four year period was not associated with an excessive incidence of morbidity or mortality In contrast, the possible significance of isolated LAD beyond −30° in twenty asymptomatic subjects was evaluated employing a graded multistage exercise test, compared to a control group of twenty asymptomatic age matched subjects with normal axis[10] Of the group with isolated LAD, ischemic ST segment changes appeared in 35 per cent and VPCs in 30 per cent, compared with respective incidences of 15 per cent and 5 per cent in the control group, both of these differences being significant. Since an ischemic response to an exercise test is strongly correlated with cardiac disease and future morbidity, LAD beyond −30° may not be a benign finding

Electrocardiograms passing through the hospital ECG station are not typically drawn from the community population at large but rather from a selected population with illnesses of varying types and degrees It was for this selected population that we studied the clinical setting in which LAD is observed, and also the frequency with which specific cardiac abnormalities can be implicated in the etiologic mechanism of LAD

Materials and methods

One hundred consecutive ECGs with LAD defined as an axis between zero and −90° in the frontal plane, were studied In each case, the clinical diagnosis was obtained, the ECG findings tabulated (Table I) based upon the following criteria

Electrical axis is a vector defined as the time averaged or mean electrical force during inscription of QRS Therefore the axis direction in the frontal plane was determined from the net algebraic area within QRS in the six standard limb leads respectively

The diagnosis of regional myocardial infarction was based upon abnormal Q waves in relevant leads such Q waves were required to be at least 0 04 seconds in duration and 2 0 mm in depth These requisite measurements would be reduced 25 per cent if definite notching of QRS occurred within the initial 0 04 second These Q wave criteria are slightly more strict than those recently employed in an evaluation of the accuracy of Q waves in the diagnosis of myocardial infarction[11] Their incidence of false positive di

selecting patients with some particular extent of inferior infarction beyond that required to produce LAD

Left anterior hemiblock The second largest ECG diagnostic category among the 100 patients with LAD was LAHB without associated evidence of infarction on ECG or clinical coronary sclerosis Of the 19 patients in this category eight showed LAHB alone nine showed LAHB with RBBB and two showed LAHB with LVH As seen in Table IV all these 19 patients demonstrated LAD to −30 or beyond but this only reflects the diagnostic criteria for LAHB which require this degree of LAD though we have observed patients with initially mild degrees of LAHB at which time the axis was directed between zero and −30 Also the two patients with LAHB and LVH were included in the present group since we have found that LVH alone rarely if ever produces LAD beyond −30 Also Table IV itself shows that LVH is an uncommon cause of LAD

Complete left bundle branch block (CLBBB) Of these 12 patients LAD between zero and −29 was present in three and beyond −30 in nine patients Since most instances of CLBBB do not show LAD but demonstrate a normal mean electrical axis i e between zero and +90 the present group of twelve patients represents a minority of patients with CLBBB Though the present study did not determine the incidence of LAD in CLBBB we estimate this incidence between 20 per cent and 30 per cent in our ECG station

Of the nine patients with CLBBB and LAD beyond −30 six showed the classical morphologic features of LAHB namely prominent initial forces directed inferiorly and slightly rightward counterclockwise vector rotation in the frontal plane and terminal forces directed superiorly in the vicinity of −60 with an s wave in Lead V_6 Thus it appears that even when the QRS duration is 0 12 seconds or longer and block is considered complete there may exist differential delays within the left bundle branch system, and when the greatest delay occurs in the anterior superior fascicle the gross morphologic features of LAHB may appear

In view of the uncertainty of diagnosing old myocardial infarction in the presence of CLBBB no attempt was made within this group of 12 patients to distinguish those in whom the conduction disturbance was associated with infarction from those who might represent primary disease of the specialized conducting system

Table V Site of infarction and degree of LAD in 43 patients

Site of infarction	Degree of LAD: 0 to −29	Degree of LAD: −30 to −90	LAHB
Septal	1	2	2
Anteroseptal	1	13	10
Anterolateral	1	0	—
Lateral	1	2	2
Inferior	6	9	
Septal and inferior	1	1	
Anteroseptal and inferior	1	3	
Lateral and inferior	0	1	
Total	12	31	

Left ventricular hypertrophy (LVH) Only two patients presented LVH as the apparent cause of LAD and in both the degree of axis deviation was less than −30 the voltage of QRS in precordial leads and associated ST T changes alone were sufficient for the diagnosis of LVH In two other patients mentioned earlier in Group 2C of Table IV LVH co existed with typical LAHB and the latter was regarded as the cause of the LAD which was greater than −30 in these cases

LAD nonspecific The twenty four patients in this group are perhaps the most interesting because the explanation for their LAD is not understood nor is its significance known This group was divided into one subgroup of sixteen patients without any other ECG abnormalities, so called isolated LAD and a second subgroup of eight patients whose ECG s showed one or more other abnormalities These abnormalities consisted of left atrial enlargement in two subjects long PR interval in one subject abnormal initial QRS forces manifest as notching slurring or poor amplitude of r waves in three subjects abnormal middle forces manifest by slurring and notching of the midportion of QRS in two subjects and nonspecific ST T changes in two subjects

Of the sixteen patients demonstrating LAD without other ECG abnormalities fourteen had an axis between zero and −29 and their age distribution was not significantly different from

Table IV ECG diagnoses and degree of LAD

Group	ECG diagnosis	Number of patients		
		Degree of LAD		
		0 to −29	−30 to −90	Total
1	Infarction	12	31	43
2a	LAHB isolated	–	8	8
2b	LAHB and RBBB	–	9	9
2c	LAHB and LVH	–	2	2
3	Complete LBBB	3	9	12
4	LVH	2	–	2
5a	LAD and other ECG abnormalities	8	–	8
5b	LAD isolated	14	2	16
	Total	39	61	100

tomatic patients referred for a routine ECG and 3 per cent occurred in patients presenting with chest pain which subsequently appeared to be noncardiac in origin

Age distribution The distribution of our 100 patients according to age (Table III) are meaningful only in relation to the ages of all patients served by our hospital's ECG station Therefore, the age distribution of the ECG patient population was determined from several hundred consecutively recorded ECG's and these percentiles used to correct those for our 100 patients with LAD, dividing the percentage of the LAD group within an age range by the percentage of the general ECG population within the same age range This ratio has an expected value of 1 0 if LAD bears no relation to age is greater than unity if LAD is positively correlated with the age category and conversely It appears that LAD is relatively uncommon below the age of forty increases in frequency thereafter, but only beyond the age of eighty years is LAD clearly more frequent than its occurrence in our entire patient population

Electrocardiographic diagnosis The general categories of the ECG findings associated with LAD appear in Table IV Old myocardial infarction was unequivocally diagnosed in 43 per cent and emerges as the single most prevalent pathologic process associated with LAD particularly when the axis deviation is beyond −30°

Myocardial infarction Analysis of these 43 patients with regard to the mechanism of LAD and its relation to the site of infarction is summarized in Table V The two principal mechanisms by which infarction produced LAD were block in the anterior division of the left bundle branch system (left anterior hemiblock or LAHB) seen in 14 patients with infarction of the septal, anterior, and/or lateral region of the left ventricle and loss of inferior forces with inferior infarction, best evidenced in 15 patients with infarction of the inferior wall only In an additional seven patients findings of inferior infarction co existed with anterior septal and/or lateral infarction in which cases both mechanisms for LAD may have been operative Also another seven patients presented LAD with septal anterior and/or lateral infarction but were not categorized as examples of LAHB due to absence of some diagnostic ECG feature However, some of these cases may indeed represent atypical forms of LAHB perhaps a partial LAHB involving only a limited number of fibers within the left anterior division

It was interesting to observe that when anteroseptal infarction produced LAD the degree of deviation was nearly always greater than −30° (13 out of 14 patients) and the mechanism was LAHB In contrast inferior infarction resulted in a more uniform distribution of the degree of LAD within the left upper quadrant of the frontal plane This is consistent with the hypothesis that the degree of LAD with pure inferior infarction is related to the amount of myocardial necrosis and the expectation that our consecutively selected group of patients would show no bias toward

anterosuperior region of the left ventricle might be expected to produce LAD Such might occur as a compensatory phenomenon in response to postero inferior infarction in which case electrocardiographic evidence of the inferior infarction would likely be present and would properly be considered as the major factor producing the LAD Perhaps more interesting is the possibility that asymmetrical hypertrophy of the anterosuperior myocardium of the idiopathic variety akin to IHSS can produce LAD in the absence of any other ECG abnormality In such instances we would still not expect LAD beyond −30 except in the most extreme cases

In the presence of LAHB the diagnosis of LVH is permissible if one relies upon the changes in precordial leads If anything LAHB tends to obscure the features of LVH With LAHB the amplitude of the R waves in Lead V_6 often seems restricted as the s wave grows larger Also the concept of the ventricular gradient generally seems operative in that the deepening s wave in Lead V_6 is accompanied by a more positive hence taller T wave an effect opposite to the depressed ST T sought in LVH Thus when LAHB is present but the features of LVH are seen in the precordial leads we feel that LVH can be diagnosed.

On the other hand, our experience shows that LAHB often produces large voltages in the limb leads—tall R wave in Leads I and aV_L and deep S wave in Lead III—in the absence of electrocardiographic evidence of LVH in precordial leads or clinical evidence of LVH Therefore when LAD accompanies such voltage increases in the limb leads alone we do not believe that LVH *should be diagnosed but rather suspect LAHB*

The prominence or degree of LAHB as manifest in clinical electrocardiograms by voltage and axis in the limb leads may be related both to the amount of delay within the fascicle *and* the number of fibers involved. The first of these namely the relation between delay time and degree of bundle branch block has been documented in RBBB As the delay in conduction within the right bundle increased progressively relative to the left bundle the degree of RBBB progressed from the appearance of a notch on the upstroke of the S wave in Lead V_1 to a small r wave characteristic of incomplete RBBB and a further delay of only 10 msec was needed to produce a broad, tall R wave typical of complete RBBB[1] Similarly the magnitude and duration of the terminal voltages in LAHB as well as their precise orientation within the left superior quadrant may be related to the delay time within the left anterosuperior fascicle which determines the extent to which the forces of the affected myocardial segment are isolated and unopposed

The second factor which could determine the prominence of LAHB is the particular anatomy of the left bundle s fascicles Rosenbaum s dissections of human *hearts consistently disclosed only* two fascicles derived from the left bundle branch terminating near the anterior and posterior papillary muscles respectively[12,18] However other anatomic studies have disclosed that in approximately 50 per cent of human hearts a third fascicle derives from the left bundle between the classical anterior and posterior divisions occupying a central septal position[19] This agrees with an earlier experimental observation that transection of both anterior and posterior fascicles would not produce complete LBBB if a collection of mid septal fibers were left intact[20] The existence of three fascicles from a functional view point is supported by observations of total excitation of an isolated human heart wherein three areas of initial excitation appeared on the left ventricular endocardium in the vicinity of the anterior and posterior papillary muscles and central septum[21] If the existence of a discrete middle fascicle is variable its presence and extent in a particular heart would effect the size of the myocardial segment excited via the anterior (and posterior) division thereby influencing the magnitude and orientation of terminal forces manifest by LAHB

LAD of undetermined cause was present in 24 per cent (Table IV Group 5) a relatively significant number that evokes comment with regard to possible mechanisms

First we suggest that some individuals with LAD between zero and −30 represent examples of mild slowing or delays of conduction within the left anterosuperior fascicle Several observations favor this hypothesis Two patients in our group of LAD of undetermined cause subsequently showed typical LAHB intermittently with further rotation of the axis beyond −30 and this has also been observed in other patients not in the present study Also conduction in the left anterosuperior fascicle like many other biologic processes subject to derangement would be expected to range from mild to severe with corre

that of the entire 100 subjects with LAD Included among these fourteen subjects are two patients with variability in the degree of LAD on serial tracings which appeared to be early, intermittent LAHB These two subjects were not placed in the category of LAHB because in each case the initial ECG which entered the patient into this study demonstrated LAD only to −15°, though a subsequent tracing demonstrated LAD beyond −30° as well as the other features of LAHB The two subjects with isolated LAD beyond −30° were asymptomatic persons undergoing routine annual evaluation One was a 45 year old nurse with LAD at −35° and the other a 37 year old policeman whose axis varied from −25° to −35° during respiration Both of these subjects may represent a form of LAHB, but were not categorized as such owing to the initial forces not being sufficiently inferior in direction

Discussion

In the absence of congenital cardiac abnormalities, LAD is a relatively rare occurrence during childhood and early adult years In our study group the incidence of LAD increased sharply beyond an age of forty years and was greatest beyond eighty years of age Similar observations were made of RBBB in 106 cases obtained from electrocardiographic findings in 67 375 asymptomatic subjects in the United States Air Force Here too the incidence of RBBB increased significantly above forty years of age and was clearly an acquired condition [13] Thus the incidence of LAD like RBBB does appear to increase with age and must be regarded as an acquired phenomenon, paralleling the increase in coronary atherosclerotic heart disease, most cardiomyopathies and degenerative processes The last is of particular interest in this regard since A V block, a conduction disturbance is often degenerative rather than atherosclerotic in origin Similarly, acquired LBBB in asymptomatic subjects should not be considered of atherosclerotic origin In 27 asymptomatic men in the armed forces whose ECG developed the pattern of LBBB, there was no evidence of heart disease upon thorough clinical evaluation, including an exercise stress test Coronary arteriography revealed that 24 of the 27 men were free of any coronary obstructions and two men each had one obstruction less than 50 per cent in locations which would not appear related to LBBB, namely in a nondominant right coronary and a left circumflex Thus in 26 out of 27 asymptomatic men the appearance of LBBB was idiopathic,[14] presumably an intrinsic disease of the conducting system LAHB without evidence of atherosclerotic heart disease classified as idiopathic was the second largest category among our one hundred patients with LAD led only by myocardial fibrosis or an old infarction This suggests that LAHB too may often be a clinical manifestation of primary morphologic disease within the conduction system

LAHB (33 per cent) either idiopathic (19 per cent) or secondary to old septal anterior and/or lateral infarction (14 per cent) was the most frequent functional cause of LAD followed by loss of viable myocardium from the inferior region (15 per cent) Because LVH rarely appeared as a cause of LAD including even the mild degree of LAD between zero and −30°, we hesitate to accept LVH as the cause of LAD beyond −30° and will not accept same if morophologic features of LAHB are also present Certain deductive reasons support this opinion Hypertension and aortic valvular disease are probably the most common causes of LVH which tends to involve all regions of the left ventricle similarly Such symmetrical or concentric hypertrophy should not deviate the electrical axis from its normally left inferior orientation This has been frequently verified by studies of patients with LVH wherein the ECG or VCG findings may have been the focal point of the report or described incidentally For example a comparison of VCG s and ECG s between 103 patients with LVH due to hypertension or aortic valvular disease and 327 patients with myocardial infarction failed to reveal any significant difference in electrical axis or orientation of the vector loop in the frontal plane Only voltage differed significantly [15] In both groups the average orientation of the electrical axis was approximately 30° Another report of moderate to severe discrete subaortic stenosis in 25 children up to age 12 years documented by cardiac catheterization with angiography in all of whom 20 underwent surgical correction because of the severity anatomic LVH of the generalized or concentric type was present in all However not one showed LAD and the axis ranged between +5° and +90 [16] In contrast an asymmetrical hypertrophy predominating in the

anterosuperior region of the left ventricle might be expected to produce LAD Such might occur as a compensatory phenomenon in response to postero inferior infarction in which case electrocardiographic evidence of the inferior infarction would likely be present and would properly be considered as the major factor producing the LAD Perhaps more interesting is the possibility that asymmetrical hypertrophy of the anterosuperior myocardium of the idiopathic variety akin to IHSS can produce LAD in the absence of any other ECG abnormality In such instances we would still not expect LAD beyond −30 except in the most extreme cases

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On the other hand our experience shows that LAHB often produces large voltages in the limb leads—tall R wave in Leads I and aV_L and deep S wave in Lead III—in the absence of electrocardiographic evidence of LVH in precordial leads or clinical evidence of LVH Therefore when LAD accompanies such voltage increases in the limb leads alone we do not believe that LVH should be diagnosed but rather suspect LAHB

The prominence or degree of LAHB as manifest in clinical electrocardiograms by voltage and axis in the limb leads may be related both to the amount of delay within the fascicle *and* the number of fibers involved. The first of these namely the relation between delay time and degree of bundle branch block has been documented in RBBB As the delay in conduction within the right bundle increased progressively relative to the left bundle the degree of RBBB progressed from the appearance of a notch on the upstroke of the S wave in Lead V_1 to a small r wave characteristic of incomplete RBBB and a further delay of only 10 msec was needed to produce a broad, tall R wave typical of complete RBBB [1] Similarly the magnitude and duration of the terminal voltages in LAHB as well as their precise orientation within the left superior quadrant may be related to the delay time within the left anterosuperior fascicle which determines the extent to which the forces of the affected myocardial segment are isolated and unopposed

The second factor which could determine the prominence of LAHB is the particular anatomy of the left bundle s fascicles Rosenbaum s dissections of human hearts consistently disclosed only two fascicles derived from the left bundle branch terminating near the anterior and posterior papillary muscles respectively [12,18] However other anatomic studies have disclosed that in approximately 50 per cent of human hearts a third fascicle derives from the left bundle between the classical anterior and posterior divisions occupying a central septal position [19] This agrees with an earlier experimental observation that transection of both anterior and posterior fascicles would not produce complete LBBB if a collection of mid septal fibers were left intact [20] The existence of three fascicles from a functional viewpoint is supported by observations of total excitation of an isolated human heart wherein three areas of initial excitation appeared on the left ventricular endocardium in the vicinity of the anterior and posterior papillary muscles and central septum [21] If the existence of a discrete middle fascicle is variable its presence and extent in a particular heart would effect the size of the myocardial segment excited via the anterior (and posterior) division thereby influencing the magnitude and orientation of terminal forces manifest by LAHB

LAD of undetermined cause was present in 24 per cent (Table IV Group 5) a relatively significant number that evokes comment with regard to possible mechanisms

First we suggest that some individuals with LAD between zero and −30 represent examples of mild slowing or delays of conduction within the left anterosuperior fascicle Several observations favor this hypothesis Two patients in our group of LAD of undetermined cause subsequently showed typical LAHB intermittently with further rotation of the axis beyond −30 and this has also been observed in other patients not in the present study Also conduction in the left anterosuperior fascicle like many other biologic processes subject to derangement would be expected to range from mild to severe with corre

sponding degrees of LAD However, contemporary diagnostic criteria for LAHB admit only LAD at −30° and beyond leaving a hiatus between zero and −30° which should correspond to milder delays of conduction within the left anterior division In fact since the electrical axis bears scant relation to anatomic position we suspect that the orientation of the electrical axis throughout the normal range of zero to +90° is a function of the relative asynchrony between excitation arising from the anterosuperior vs postero inferior divisions, respectively, of the left bundle branch Recall that delays in the postero inferior division produce right axis deviation in contrast to LAHB Just as LAHB is much more common than LPHB mild LAD is much more frequent than mild RAD with or without any degree of right bundle branch block, in electrocardiograms which are unremarkable in all other respects This too may simply reflect the greater vulnerability of the thin discrete anterosuperior division to the vicissitudes of cardiac morbidity than either the left postero inferior division or the right bundle branch

Second we suggest that in some individuals with LAD between zero and −30° the cause is an asymmetrical hypertrophy of the anterior superior wall of the left ventricle, to be categorized with hypertrophic subaortic stenosis and the more recently described asymmetric septal hypertrophy or myocardial hypertrophy without outflow tract obstruction In the monograph by Braunwald[22] describing sixty four patients with IHSS a normal axis was present in forty four (69 per cent) However LAD between zero and −90° was present in fourteen (11 per cent) of which six were between zero and −30°, and these may represent patients whose hypertrophy was sufficiently asymmetric with predominance in the anterior superior region to produce LAD Thus LAD may be a clue to asymmetric hypertrophy in a patient with precordial discomfort unexplained breathlessness, or other symptoms and signs which have been described in the idiopathic hypertrophic cardiomyopathies

Like other ECG abnormalities the clinical significance of LAD would appear to be that of the underlying etiologic process As a manifestation of a mild aberration of conduction within the left anterosuperior fascicle, LAD probably carries the same benign prognosis generally attached to RBBB in the adult [13] When LAD is the result of ischemia an exercise ECG would seem useful in identifying such instances and the prognosis determined by the coronary atherosclerotic process

Summary

Clinical and electrocardiographic findings were analyzed in 100 consecutive cases of LAD Below the age of forty years LAD was uncommon, but its incidence increased continuously thereafter The most frequent primary clinical diagnosis was arteriosclerotic heart disease The functional mechanism producing LAD most often was LAHB responsible in about 40 per cent. Approximately half the instances of LAHB were associated with old myocardial infarction of septal, anterior or lateral regions, but half were seen in the absence of infarction or clinical coronary sclerosis and are presumed due to primary degenerative processes within these specialized conducting fibers Approximately one sixth of the instances of LAD were due to loss of inferior forces following inferior myocardial infarction Typical left ventricular hypertrophy was a distinctly *un*common cause of LAD Last in 24 patients with LAD the mechanism or cause was not evident initially, of which two were subsequently shown to represent a very mild degree of LAHB Also it is suggested that asymmetric myocardial hypertrophy of the anterior wall may account for some instances of LAD not otherwise explained

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Pseudocoarctation or congenital kinking of the aorta radiologic considerations

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Pseudocoarctation of the aorta is a rare malformation which can be interpreted as an abnormal elongation of the aorta in the superior mediastinum The course of the aorta is hence tortuous consisting of an ' S ' shaped or figure '3 bending and double kinking of this vessel

We report five cases of this malformation three of which occurred in children

Case reports

Case No 1 A six year old child presented with an isolated systolic murmur best heard at the base and known since six months of age On chest x ray in the frontal plane the heart appears normal but the aorta is elongated with an abnormally high aortic arch and the great vessels have the so called chimney like pattern described in coarctation

X ray of the barium filled esophagus shows a double notch on the left border as seen in coarctation with poststenotic dilation

Selective angiocardiography in the pulmonary artery shows an image which evokes on frontal view a coarctation but on lateral view the aortic arch is tortuous and looks like a figure three whose middle portion is at the level of the ligamentum arteriosum

Aortography by right axillary artery reveals moderate dilatation of the ascending aorta with a double indentation on the descending aorta the most distal one looking like a coarctation (Fig 1) but there is no poststenotic dilatation The left subclavian artery is markedly dilated The lateral view is very characteristic with the image of 3 without stenosis (Fig 2)

In conclusion it is an isolated pseudocoarctation without any other cardiac anomaly and no treatment is necessary

Case No 2 A 27 year old adult presented with chest pain. He has systolic murmur best heard over the pulmonic area irradiating under the left clavicle and to the back. No other abnormality was found. Frontal chest x ray reveals an aortic arch which was somewhat high and bulging with a dilated descending aorta X ray of the barium filled esophagus showed a double notch the superior one is related to a dilatation of the aortic arch Selective angiocardiography in the pulmonary artery shows marked dilatation of the ascending aorta and a pattern of pseudocoarctation which mimics the first case The aortic arch is very high reaching the third dorsal vertebra and the origin of the left subclavian artery is very dilated Since puncture of the axillary artery could not be performed a retrograde aortic catheterization was done through the femoral artery The pseudocoarctation could not be crossed and aortography was done at the level of the pseudocoarctation The aortic arch was opacified by counter current flow The abnormality was visible which evoked on frontal view (Fig 3) a coarctation with poststenotic dilatation while on the lateral view (Fig 4) the figure 3 pattern was outlined The origin of the left subclavian artery was very dilated The right subclavian artery was aberrant and looked like a lusoria arteria

In conclusion a diagnosis of kinking associated with an aberrant right subclavian artery is made in a 27 year-old patient

Case No 3 A 12 year old male is admitted who presented with a long standing systolic murmur first evoking an endocardial cushion defect Frontal chest x ray shows an elongated aorta with a chimney like pattern a large heart with an elevated apex a rounded left inferior segment and a concave middle heart segment Pulmonary vasculature is moderately increased Retrograde catheterization of left chambers was performed from the femoral artery Left ventriculography (Fig 5) shows a small and high ventralseptal defect (VSD) with an aneurysm of the membranous septum a dilated and deformed right sinus of Valsalva and aortic kinking with large right and left subclavian arteries The malformation is seen better on lateral view than on frontal view The aortic arch is high reaching the third dorsal vertebra The figure 3 pattern is outlined There is no poststenotic dilatation and no aortic gradient

In conclusion a 12 year old child has several malforma

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Fig 1 Pseudocoarctation of the aorta in a 6 year-old child. Double notch on descending aorta the most distal mimicking a coarctation



Fig 2 Pseudocoarctation of the aorta (same case as Fig 1) Aortography through the axillary artery lateral view showing a very typical figure 3 pattern without stenosis

tions of the heart with a pseudocoarctation of the aorta best seen on lateral view of angiography

Case No 4 A 5 year-old male presented with a low-grade systolic murmur at the base without any other findings Chest x ray shows an enlarged superior mediastinum and a notch on the left border of the esophagus Frontal view of angiocardiography from the pulmonary artery shows on levophase a slightly dilated ascending aorta which evoked a supravalvular aortic stenosis or aortic kinking Retrograde



Fig 3 Pseudocoarctation in a 27 year old adult with poststenotic dilation mimicking a coarctation on frontal view

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Fig 6 *A* and *B* Pseudocoarctation in a 5 year old child. Left ventriculography in left anterior oblique and lateral views outline of pseudocoarctation of descending aorta at its origin Dilation of ascending aorta

and fixed at a certain point The caliber of the aorta is not markedly changed but it is slightly irregular with moderate dilation proximally and sometimes distally

Clinically pseudocoarctation may be isolated presenting with a systolic murmur at the base and probably related to the frequent dilation of the ascending aorta or it can be revealed by an abnormal vascular opacity on chest x ray Sometimes the pseudocoarctation is discovered incidentally among other abnormalities

Radiologic features

Frontal view of chest plain film Three main types can be differentiated.

FIRST TYPE. The elongation of the aortic arch gives an abnormally high aortic arch This is more frequent in children where the aortic arch is not very prominent and where the image of the chimney shaped aorta with the opacity of the great vessels stretching upward and tapering off is seen (Cases 1 and 3)

SECOND TYPE It is frequent in adults Three varieties of images can be seen (1) *image of a double opacity* an oval left superior mediastinal opacity pulsating and not very dense is located above a second opacity well delineated corresponding to the normal aortic knob This second opacity is situated after kinking Its left border



Fig 6 C. Marked notch on the left border of the esophagus



Fig 4 Same case as Fig 3 On this lateral view the figure 3 pattern is outlined

catheterization of the left heart was performed from the femoral artery Opacification of the aorta confirmed the supravalvular dilatation of the ascending aorta and the outline of pseudocoarctation of the descending aorta (Fig 6) at its origin just distal to the aortic isthmus There was no dilatation of the vessels of the neck There were no pressure gradients

In conclusion a 5 year old child has a minor aortic dysmorphy with mild kinking

Case No 5 A 19 year old female presented with Turner s syndrome and a congenital heart defect known for several years She has a systolic murmur best heard over the aortic area with irradiations to the apex Chest plain film shows on frontal view (Fig 7) a rounded left inferior segment The aortic knob is abnormally prominent Roentgenogram of the barium filled esophagus shows on the frontal view a double left notch one at the level of the normal aortic knob the other discretely above it Oblique and lateral views show a marked posterior notch Right heart catheterization shows an abnormal pulmonary venous return in the superior vena cava without an atrioseptal defect (ASD) During catheterization of the aorta through the right femoral artery it is difficult for the catheter to cross the ascending aorta There is no real gradient of pressure Angiography on frontal (Fig 8) and lateral (Fig 9) views from the left ventricle reveals a VSD and a pseudocoarctation well seen on frontal and lateral view with dilatation of the ascending aorta Intravenous pyelogram (IVP) shows megacalyces

In conclusion a 19 year old female has Turner s syndrome a left to right shunt and aortic kinking

Discussion

Pseudocoarctation of the aorta is known since 1951 and about 150 cases have been reported up to now Adult males are mostly affected However some cases have been reported in children [1,9,32,33] at the age of 7 5 [23] with seven cases ranging from 1 month to 13 years of age [19] four cases of two months to 12 years of age We have three cases between five and twelve years of age This entity has similarities mainly to coarctation especially from the radiologic point of view but it can be differentiated by the following criteria (1) no stenosis of the aortic lumen (2) no gradient of pressure above and below the malformation and absence of collateral arteries and (3) no surgical treatment



Fig 5 Pseudocoarctation in a 12 year-old male Lateral view of left ventriculography aneurysm of membranous septum ectasic right sinus of Valsalva and kinking of the aorta with dilated subclavian arteries.

Pseudocoarctation is secondary to an abnormality of evolution of the aortic arches in the same way as true coarctation Its origin is an elongation of the fourth aortic arch and consequently an abnormally high aortic arch Moreover this dilated artery has only a small space in which to develop and it is fixed at the level of the ligamentum arteriosum It is easy to imagine the abnormal course of this vessel which is too long



Fig 8 Same case as in Fig 7 Left ventriculography frontal view Pseudocoarctation with dilation of ascending aorta



Fig 9 Same case as in Fig 7 Left ventriculography lateral view Pseudocoarctation with dilation of ascending aorta

This is not seen in coarctation because the aortic arch is of normal length

(3) *Image of very dense opacity of the aortic knob* this image corresponds to the dilation distal to the kinking and is often mistaken for an aneurysm of the descending aorta It is, therefore necessary to follow very carefully the border of the aorta as described above

THIRD TYPE In such cases the chest plain film does not evoke kinking because it is very moderate The image of the great vessels is normal

Oblique view and lateral view of the chest plain film According to Nasser[22] lateral view and especially an oblique view shows the sharp kinking of the posterior border of the aorta with a figure 3 image However such a pattern can be seen in coarctation of the aorta where the posterior border also has marked indentation in the oblique view Therefore it is necessary to follow the anterior border of the aorta which is difficult if laminography is not done

Mediastinal tomography Only a few authors have done tomographies Pattinson and Grainger[24] and Faivre and co workers[11] have done tomographies in lateral view which revealed the image of the buckling of the aorta However in our cases tomographies were of no use In children especially they are not very useful because the aorta is not sufficiently dense and thick In adults the diagnosis of the abnormal course of the aorta may be easier if there is atheromatous calcifications of the wall[1,21,22,32,33]

Roentgenogram of the barium filled esophagus Instead of a single normal aortic knob two notches on the left border corresponding to the bulges of the double knee can be seen Fairly often the inferior notch is the most visible beyond the aortic knob This is due to the dilation after the malformations (Cases 1 and 4) or to the sinuosities of the descending aorta[3] Moreover the roentgenogram of the esophagus is useful for the diagnosis of aberrant arteries (Case 2)

Angiography Several approaches can be used. Of course the arterial approach is the best one



Fig 7 Turner s syndrome with pseudocoarctation in a 19 year old patient *A* Plain chest film shows on frontal view a bulging of aortic knob *B* and *C* oblique and lateral views show a marked posterior notch

may be more or less accentuated because of the sinuosity or because of a possible dilation [3]

(2) *Image of a high mediastinal opacity* such a pattern corresponds to the bulging of the aorta just above the insertion of the ligamentum arteriosum This image looks like a left superior mediastinal tumor located above the aortic knob which is considered as normal [5 7 22 27 30]

Sometimes, this opacity is erroneously taken for the aortic knob One must keep in mind that normally the superior contour of the aortic arch is separated from the inferior border of the medial extremity of the left clavicle which may however sometimes be close to the aorta if the film is not taken during a forced inspiration Moreover if there is a doubt an important sign is to follow the lateral border of the ascending aorta which courses well above the inferior border of the right clavicle and above the superior border of the sternum in cases of pseudocoarctation

some years later This is the opinion of some authors[12 19 28 37] who judge it necessary to follow patients having aortic kinking with chest films at regular intervals Gay and Young[12] and Turner and co workers[37] reported cases of association of pseudocoarctation with aortic aneurysm above or below the malformation They believe that it is more a complication than an association Turner and co workers[37] have supported this belief by successive angiograms showing development of an aneurysm in a 36 year old patient 12 years after kinking was first diagnosed on angiography A patient of Gay died of a ruptured aneurysm two years after the diagnosis of pseudocoarctation was made Turner and co workers[37] believe that the aortic wall loses its elasticity Consequently the aorta enlarges and an aneurysm can appear Often the caliber of the aorta is enlarged on both sides of the kinking without any real aneurysm to speak of

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Table 1 Congenital kinking of the aorta

Age	Aortic arch	Left border of the esophagus	Left angiogram	Associated defects
6 years	High chimneylike	Double notch	Sinuosities of the aorta	—
27 years	Slightly high	Double notch	Marked kinking	Aberrant right subclavian artery
12 years	High chimneylike		Kinking	High VSD Ectasia of sinus of Valsalva Large subclavian artery
5 years	Left superior vena cava	One notch	Mild kinking	—
19 years	Bulging of aortic knob	Double notch	Kinking	Turner s syndrome Abnormal pulmonary venous return VSD Megacalyces

because it is possible to measure the pressures on both sides of the kinking Femoral puncture is the easiest method and has been used in four of our cases However, at times the catheter cannot be passed through the defective zone and this should arouse suspicion of a pseudocoarctation The axillary approach is better On the right side it is easy to introduce the catheter into the left ventricle and evaluate the associated defects but the buckling can be better crossed from the left side and this is the preferred method

The best positions in which to see the buckling of the aorta are the lateral view and the left anterior oblique view On frontal view the aorta has *one or two notches which evoke a coarctation* without dilation before or after the notches and without any stenosis and no collateral arteries The aortic arch is elongated and arises higher than the clavicle and this is an important difference with coarctation

On lateral or oblique view the kinking is more visible, showing a figure 3 pattern whose middle segment is at the level of the *ligamentum arteriosum* The caliber of the vessels is normal Proximally and distally to the kinking moderate dilations can be seen Rarely they are aneurysmal pouches A simple dilation can even give rise to an aneurysm [37] It is important to know that there usually is no pressure gradient or at least one which is less than 20 to 25 mm Hg above and below the kinking

THE ASSOCIATED DEFECTS The ascending aorta is frequently dilated (Cases 1 3, 4, and 5) in the absence of an associated aortic stenosis The abnormalities of aortic arches are very frequent which proves that pseudocoarctation results from an abnormality of the aortic arches. They include arteria lusoria (Case 2), patent ductus arteriosus or abnormalities of the left subclavian artery which is often very dilated and tortuous [19 41] Other malformations include aneurysms of the aortic sinus of Valsalva [14 19 32-33] Still other malformations have been noted aortic valvular stenosis [19 23 32 33] VSD [8 19 23] and corrected transposition of great vessels [32 33]

Sometimes pseudocoarctation is part of a syndrome of complex malformations Turner s syndrome [18 36 39] Noonan's syndrome [23] and Hurler s syndrome [23]

Differential diagnosis Pseudocoarctation must be completely differentiated from the moderate degree of coarctation not sufficient to give hypertension and collateral arteries but which consists of stenosis of at least one third of the aortic caliber without any abnormality of its course However coarctation and pseudocoarctation may be associated [1,20]

From the radiologic point of view, the differ*ential diagnosis on* a plain chest film includes (1) a left superior mediastinal tumor (2) an aneurysm of the aorta and some dilations of the aorta as seen in dystrophies of the connective tissue in children (Marfan s disease Lobstein s disease Hurler s disease and Ehlers-Danlos syndrome) in adults the sinuosities of arterioselerosis are usually located lower on the descending aorta *and (3) true coarctation* where there are costal notches and where the image of the great vessels does not reach the clavicle

Course of the abnormality Isolated kinking is an asymptomatic abnormality requiring no treatment However an aneurysm can occur

A comparison of timolol and propranolol in essential hypertension

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Beta adrenergic receptor site inhibitors have been used experimentally and clinically for the treatment of hypertensive diseases for well over one decade [1] Some of these drugs like propranolol share additional pharmacologic actions which may not necessarily be common to all beta adrenergic blocking compounds Thus *propranolol* alprenolol, oxprenolol, INEPA and the dextro isomers of several of these agents demonstrate certain myocardial membrane stabilizing (or quinidine like) actions as well as local anesthetic effects which have been termed non pecific and have been *suggested to be* responsible perhaps for the antihypertensive action Indeed these *experimental studies have* shown that the antihypertensive action of propranolol seemed more closely related to quinidine than to the other beta blocker sotalol which is without these *nonspecific* effects [2] In addition to this rather broad array of beta adrenergic blocking compounds *which have* been shown to possess antihypertensive properties are several other beta blocking compounds (e g pindolol sotalol, and timolol) which demonstrate a minimal degree of nonspecific actions and two other agents practolol and tolamolol, which possess only cardioselective beta adrenergic receptor inhibiting properties When the *new* beta adrenergic receptor *blocking compound* *timolol* having essentially no membrane stabilizing effects and no nonspecific effects became available it was of interest to determine whether this compound was effective as an antihypertensive agent and how this agent compared with propranolol as an antihypertensive *drug*

Methods

Patients with essential hypertension *who had* been evaluated completely were selected for this study if they satisfied certain criteria We had previously *shown that* hypertensive patients with a *hyperkinetic circulation* or an increased cardioaccelerator response to the intravenous in*fusion of* the beta adrenergic agonist isoproterenol were more likely to respond with a reduction of arterial pressure to a beta adrenergic blocking drug [3] and therefore we included these criteria for the preselection of patients We also included that obvious group of patients who *had responded* previously to propranolol antihypertensive therapy

The first part of this study concerned fourteen *patients* with mild to moderately severe essential hypertension who were selected to compare *timolol with* a placebo in a double blind fashion As with the patients in the second part of this study all were required to provide their *written* informed consent in conformity *with the* princi*ples of the* Code of Helsinki and our own institu*tional human* rights committee Each patient was asked to discontinue all therapy (*including* diuretics) for at least four weeks (if he was on therapy) and during this *time* he obtained and recorded his blood pressure at home twice daily in the supine and standing positions During a second four *week period* the patient was given a placebo capsule to take three times daily Then for the *ensuing* five weeks the patients were randomly selected for the double blind *procedure*

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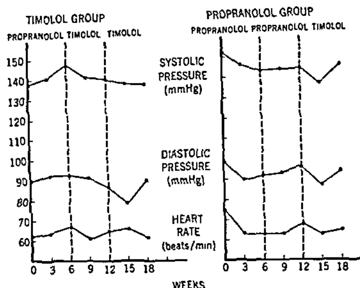


Fig 1 Average responses of systolic and diastolic pressure and heart rate obtained in the physician's office of patients during Part II of this study Each point represents the average for the six patients in each group

Table III *Timolol vs propranolol in study of response of home pressures (mm Hg)*

		Timolol group		*Propranolol group*	
	Week	*Supine*	*Standing*	*Supine*	*Standing*
Propranolol	Initial	139/82	139/93	142/87	140/94
Propranolol	3	139/84	140/91	136/79	140/87
Propranolol	6	140/83	140/90	133/88	137/84
Double blind	9	136/84	136/89	134/79	137/86
Double blind	12	137/83	138/89	133/77	135/84
Timolol	15	133/82	134/88	130/76	133/83
Timolol	18	135/82	133/89	130/76	133/83

or placebo (six patients) were compared, therefore with average pressures obtained during the initial six week period of propranolol treatment (Table II) Thus both systolic and diastolic pressures at home were reduced significantly by 14 per cent and every patient demonstrated this pressure reduction with propranolol. In general there were no differences in the average pressure or heart rate responses of the two groups of patients receiving either timolol or propranolol during the three periods—the initial six weeks of propranolol the six week double blind period and the final six weeks when the patients received timolol (Fig 1) In addition there were no differences in the average pressures when measured *at home* during the three treatment periods in the two groups (Table III) *although the pressures at home were* (on the average) approximately 10 mm Hg lower than pressures taken in the office Furthermore when the home arterial pressure responses of the 12 patients to propranolol (initial period) were compared with the timolol responses (final period) a remarkably direct correlation was observed (Fig 2)

In addition certain subtle (but significant) differences between the pressure response to the two beta adrenergic blocking drugs were demonstrated when we compare the office and home pressures during the initial six week period when the patients received propranolol and the final six weeks when they received timolol. While no significant differences with respect to the two beta blocking drugs were detected when the *office pressures* were compared, the home pressures did reflect a significant differences in systolic and diastolic pressure when recorded in either the supine or standing positions (Table IV) Thus while receiving timolol therapy home pressures

Table I Study of average responses to either timolol or placebo

	6 Placebo group (mm. Hg)		4 Timolol group (mm. Hg)	
	Placebo	Double blind	Placebo	Double blind
Home pressures				
Supine	152/96	148/95	147/94	131/81
Standing	164/103	150/103	140/100	128/90
Office pressures				
Sitting	153/100	150/99	146/98	127/85
Standing	151/104	151/103	146/107	130/90
Office heart rate				
Sitting	83	82	88	64
Standing	91	89	100	69

Table II Effect of propranolol (120 mg daily) on home pressures in 12 hypertensive patients

	Pressure (mm. Hg)				
	Control	Propranolol	Δ	t	p<
Systolic	161	138	23	4 21	0 01
Diastolic	100	86	14	6 40	0 001

Control represents most recent weekly pressure average either when receiving placebo 6 patients or no capsules 6 patients

receiving either timolol or placebo During this five week period the dosage of the capsules was increased twofold if the office diastolic pressure was not reduced by at least 10 mm Hg or if the diastolic pressure remained in excess of 90 mm Hg Thus the highest possible daily dose of timolol was 30 mg and the lowest dose 15 mg During this entire follow up period (and for the second part of this study also) the patients continued to take their own pressures at home were instructed to call upon the monitoring physicians for any reason and at any time had pill counts in the office at their weekly visits and had frequent checks of their complete blood counts, urinalysis blood chemistry and electrocardiogram

The second part of this study concerned sixteen patients with essential hypertension of mild to moderate severity of vascular disease some of whom had been the subjects of the first part of this report All were selected on the basis of having responded to previous antihypertensive therapy with propranolol Since most had been receiving propranolol immediately prior to this study, and since the object of this study was to compare the antihypertensive efficacy of propranolol with timolol, the initial six weeks involved treatment with propranolol (one 40 mg capsule three times daily) This period was followed by the double blind segment also lasting for six weeks, during which time the patient received either propranolol (120 mg daily) or timolol (30 mg daily) in three divided doses

Results

Of the fourteen patients who began the first study (timolol vs placebo) ten completed two patients withdrew during the initial placebo control period and two were started on known antihypertensive therapy because their pressures became too high to permit them to remain off all antihypertensive therapy for the potential time period of 13 weeks Of the ten patients who completed the study six received placebo and only four received timolol However each patient who received timolol demonstrated a fall in home and office pressures associated with a significant reduction in heart rate (Table I) Thus while the average supine and standing home pressures failed to change in those patients receiving placebo there was a significant reduction in systolic and diastolic pressures in both positions in those patients receiving timolol and this represented a 13 per cent reduction in supine mean arterial pressure

Twelve of the sixteen essential hypertensive patients who began the second part were able to complete the study One, who had received propranolol during the double blind phase of the study died during this phase because of an acute dissection and rupture of his atherosclerotic abdominal aortic aneurysm One patient was excluded from analysis because of an error in medication and two patients failed to return for follow up during the study Of the remaining twelve patients six received timolol and six propranolol during the double blind phase of the study

In order to compare the effectiveness of timolol therapy with propranolol it was necessary to demonstrate a significant reduction of pressure on propranolol treatment with respect to pretreatment pressures Average home pressures obtained during a one month period when these patients received either no therapy (six patients)

the effectiveness of the angiotensin vascular receptor inhibitors in those hypertensive patients in whom angiotensin excess was demonstrated and in whom angiotensin was participating most in the maintenance of the elevated pressure Hence using this same logic it seems just as meaningful to evaluate the antihypertensive effectiveness of beta adrenolytic compounds in those patients in whom the inhibition of pressor mechanisms subserved by beta adrenergic receptor stimulation might similarly maintain the elevated arterial pressure

The present study then demonstrates that arterial pressure was significantly reduced in those hypertensive patients who were treated with *timolol* This reduction of arterial pressure seemed to be just as effective as that with propranolol when the compounds were used in 30 to 120 mg daily dosages respectively Thus the antihypertensive effectiveness of timolol was approximately four times as great as propranolol on a weight basis And when we increased the propranolol dosage so that the ratio was 1 8 rather than 1 4 we found no further effectiveness of the propranolol

That timolol was just as effective in reducing arterial pressure as propranolol indicates that the fall in pressure with propranolol was mediated through a mechanism subserved by inhibition of beta adrenergic receptor sites rather than through its nonspecific or membrane stabilizing characteristic This is because timolol only shares the beta receptor blocking effect of propranolol this agent seems practically devoid of the membrane stabilizing effect. Still possible however is that both agents act through a mechanism which is not mediated by beta adrenergic receptor site inhibition This might occur through an inhibition or excitation of certain central vasomotor excitatory or inhibitory sites respectively in the brain Alternatively it may still be possible that certain metabolites of both compounds may in themselves be vasodepressors

These studies also indicate that in addition to providing important information demonstrating the efficacy of antihypertensive compounds home pressures obtained by the patient may be an extremely sensitive method for assessing comparative responses of similar antihypertensive drugs. Thus by obtaining home pressures it is possible to obtain day to day measurements which may be more consistent with the patient s usual activities thereby including some of the more short term changes not seen when pressures are obtained only in the physician s office or in the clinic

None of the patients demonstrated any significant abnormality in the complete blood counts urinalysis and blood chemistries (the latter including hepatic and renal function studies) One patient was forced to discontinue timolol therapy during the second three weeks of the timolol (double blind) period in the second study because of severe abdominal cramps This reappeared when she was rechallenged with timolol this adverse effect did not occur at any time during propranolol therapy (which she has taken for over three years) Aortic dissection and rupture occurred in one patient who was receiving propranolol His arterial pressure was in good control at the time indeed this form of therapy has been generally recommended for patients with aortic dissection in order to inhibit the shearing hemodynamic forces of blood[9,10] and *especially* when surgical intervention is not indicated or when cardiac function is not significantly impaired.

Summary

The antihypertensive efficacy of a new beta adrenergic receptor inhibiting compound timolol (MK 950) was evaluated using two treatment protocols double blind timolol vs placebo treat*ment* and double blind timolol vs propranolol (10 and 12 patients respectively) These studies indicate that timolol significantly and safely reduced arterial pressure in mild to moderately severe essential hypertensive patients The reduction in mean arterial pressure with timolol was equiva*lent to* the pressure reduction with propranolol when the doses of 30 and 120 mg per day respectively were used.

The timolol and propranolol used in these studies were generously provided by Merck Sharp & Dohme and Ayerst Pharmaceutical Companies respectively Dr Lohmoller completed this work during *an Ayerst Research* Fellowship We also gratefully acknowledge the secretarial support of Mrs Elizabeth Murray

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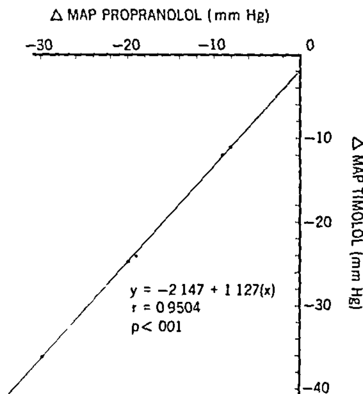


Fig 2 Correlation of the change in mean arterial pressure while receiving propranolol (120 mg per day) and timolol (30 mg per day) Each point represents the average pressures for one of the fourteen patients so treated

were significantly lower statistically (if not physiologically) In order to determine whether this difference reflected a factor of time at the conclusion of the 18 week study all twelve patients who had been receiving timolol during the final six weeks were then restarted on propranolol therapy (120 mg daily) Once more when the average home pressures during the final six weeks of timolol therapy were compared with the more recent (or the initial) six weeks of propranolol therapy both systolic and diastolic pressures were significantly lower (statistically speaking) when the patients received timolol (Table V) Further at the conclusion of this study we finally increased the dose of propranolol from 120 to 240 mg daily and found no further significant reduction in average home pressures (although the variability of the pressures was greater than during the previous six weeks therapy at the lower dose)

Table IV Comparison of pressures during initial (propranolol 120 mg daily) and final (timolol 30 mg daily) 6 week periods

	Sitting (mm. Hg)		*Standing (mm. Hg)*	
	Systolic	*Diastolic*	*Systolic*	*Diastolic*
Office pressures				
Propranolol	145	93	145	99
Timolol	141	89	142	95
t	1 6	1 4	0 9	1 4
p<	ns	ns	ns	ns
Home pressures				
Propranolol	137	83	139	89
Timolol	131	80	133	86
t	4 9	4 8	3 9	4 2
p<	0 001	0 001	0 01	0 01

Table V Comparison of home pressures during final (timolol) period (30 mg daily) and subsequent period when patient received propranolol (120 mg daily)

	Pressure (mm. Hg)				
	Timolol	*Propranolol*	Δ	*t*	*p<*
Systolic	131	135	4	3 8	0 01
Diastolic	80	84	4	2 0	0 001

Discussion

The results of these clinical studies indicate that timolol a new beta adrenergic receptor site inhibiting drug without nonspecific membrane stabilizing effects significantly reduced arterial pressure in certain selected patients with essential hypertension Because of the potential adverse effects of initiating this form of therapy in all hypertensive patients only those who were deemed most likely to respond to beta adrenergic blocking therapy were studied This is not to suggest that this form of therapy should be restricted only to those hypertensive patients with mild to moderately severe essential hypertension or to only those patients with a hyperkinetic circulation or even those who demonstrate increased cardioaccelerator responsiveness to beta adrenergic receptor stimulation However we believe that in these early clinical investigative studies patients should be studied with as similar clinical and physiologic characteristics as possible Thus it seems to us more logical to evaluate the antihypertensive characteristics of a compound when the pressor mechanisms operative in the patients are more homogeneous For example, we might make this point clearer if we extrapolate this concept to another class of antihypertensive compounds under present clinical investigation Thus one could best demonstrate

Cardiac pathology after aortic valve replacement using Hufnagel trileaflet prostheses a study of 20 necropsy patients

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Of the various prostheses used to replace mal functioning cardiac valves several have had ex tensive clinical evaluation but only a few have been examined systematically at necropsy In the pathology laboratory of the National Heart and Lung Institute cardiac morphologic findings have been described in nearly 300 patients dying after valve replacement using Starr Edwards prosthesis [1] or tissue valves [2] During the past eight years the hearts of 81 patients dying after cardiac replacement using trileaflet (20 patients) or disc valves (61 patients) also have been ex amined by us This report describes necropsy ob servations in the 20 patients who died after replacement of the aortic valve with a trileaflet prosthesis consisting of three self suspended flex ible cusps made of polypropylene and covered by silicone rubber (Fig 1) [3] No previous reports describing morphologic alterations in this partic ular prosthesis have appeared.

Patients studied

Clinical and pathologic findings in the 20 pa tients are summarized in Tables I and II Seven patients died within two months of operation (early deaths) (Table I) and 13 patients at later periods up to 58 months (late deaths) (average 22 months) (Table II) In 18 patients only the aortic valve was replaced in the other two the mitral valve also was replaced, a discoid valve[4] being utilized in each The 20 patients ranged in age at death from 26 to 76 years 13 were men and seven were women All but two patients were in functional class III or IV before valve replace ment

Of the 20 patients 17 had stenotic and three had purely incompetent aortic valves. The aortic valves were congenitally malformed in six pa tients one had a quadricuspid valve.[7] The re maining 14 patients seven of whom also had anatomic disease of the mitral valve, had three cuspid aortic valves The etiology of the valve le sions in the seven patients with associated mitral disease is considered rheumatic[8] the cause is un certain in four and degenerative in origin[9] in three

Significant (> 75 per cent) luminal narrowing of at least one of the three major (right left cir cumflex and left anterior descending) coronary arteries occurred in three patients (Patient No 1 Table I Patients Nos 9 and 10 Table II) and was the cause of death in one This patient (No 9 Ta ble II) died of an acute myocardial infarction 23 months after valve replacement She was the only patient dying six months or longer after valve replacement without evidence of prosthetic degeneration or thrombosis

Early deaths

Of these seven patients three died within one week and all seven within three weeks of opera tion. None died on the day of operation Exten sive thrombus formation (Fig 2) on the prosthe ses with obstruction to a coronary arterial ostium and myocardial necrosis caused death in four pa tients two of whom also probably had some pros

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valve replacement

A V size inside diameter (mm.)	MV operation	Implantation period (days)	Major cause of death	Status of prosthetic aortic valve						Heart weight (Gm.)	LV scarring (SE) (TM)
				Tears	AR	Thrombus	AS	COO	Emboli		
22	0	1	Bleeding	0	0	0	0	0	0	480	SE
24	0	2	AMI	0	0	+	0	+	0	600	SE
22	A	5	MR†	0	0	0	0	0	0	900	0
16	0	8	AMI	0	0	+	+	+	+	470	SE
16	0	15	AMI	0	0	+	+	+	0	580	0
18	R (disc)	16	Hemolysis massive	0	0	0	0	0	0	700	SE
18‡	0	17	AMI	0	0	+	0	+	+	520	SE

C = c mm ssu tomy CHF = ngest heart fa lu e COO = coron y ostial clusion F = fem le LA = left atrium LV = l ft entri le M = male perat n PSG = p k systol g adi nt R = repl ment SA = system c artery SE = ubendocardial TM = t nsmu l

valve replacement

MV Operation	Implantation period (months)	Major cause of death	Status of prosthetic aortic valve						Infection	Peribasilar AR	Heart Weight (Gm.)	LV scarring (SE) (TM)
			Tears	AR	Thrombus	AS	COO	Emboli				
A	21	AR	0	0	0	0	0	0	0	+	530	0
C	6	AR	+	+	0	0	0	0	0	0	490	0
O	7 5	AR	+	+	0	0	0	0	0	0	600	SE
O	12	Sepsis	+	+	+	0	0	+	+	+	480	TM
A	15	AR	+	+	0	0	0	0	0	0	850	SE
O	18	AMI	0	0	+	+	+	0	0	0	600	SE
R (disc)	18	AR	+	+	0	0	0	0	0	0	450	SE
O	19	AR	+	+	+	0	0	0	0	0	700	SE
O	23	AMI	0	0	0	0	0	0	0	0	470	TM
O	32	Aortic dissection	+	+	+	0	0	0	0	0	380	SE
A	35	AMI	0	0	+	+	+	+	0	0	690	TM
C	36	AR	+	+	+	0	0	+	0	0	900	SE
O	58	AMI	0	0	+	+	+	+	0	0	700	SE

implantation periods of six months or longer the aortic prosthesis in eight was torn (Figs 3 and 4) severely incompetent and responsible for death (seven patients) or reoperation (one patient) no degeneration of prosthetic material was evident in the other four patients despite long (18 to 58 months [average 29]) implantation periods but three had large thrombi (Fig 5) within the prosthetic sinuses causing obstruction to at least one coronary arterial ostium Histologic examination of the thrombotic material from several patients disclosed it to consist predominantly of fibrin and platelets with only a few erythrocytes Thus it was a so called white thrombus The one patient without prosthetic degeneration or thrombosis died of an acute myocardial infarction from severe coronary atherosclerosis 23 months after valve replacement All patients were discharged from the hospital on warfarin sodium

Renal hemosiderosis the anatomic indicator of intravascular hemolysis (in this case the result of trauma to erythrocytes traversing prosthetic aortic valves[10]) was sought for in the late death cases The kidneys in 11 of the 13 patients dying

Table I Clinical and necropsy data in patients dying early (< 2 months) after Hufnagel tri leaflet aortic

Necropsy No	Age (years)	Sex	Functional class (NYHA)	No A V cusps	Preoperative valve lesions				LV-SA PSG (mm. Hg)	LA LV MDG (mm. Hg)	Date AVR (mo./year)
					AS	AR	MS	MR			
1 69A 135	59	M	IV	3	+	+	0	0	↑*	0	3/69
2 67A 549	61	M	IV	1	+	+	0	0	20	0	10/67
3 68A 435	43	M	IV	3	+	+	0	+	↑*	0	8/68
4 69A 345	60	F	IV	2	+	+	0	0	80	0	7/69
5 69A 451	50	F	III	3	+	+	0	0	100	0	9/69
6 69A 497	54	M	IV	3	+	+	+	+	35	15	9/68
7 68A 577	51	F	III	4	0	+	0	0	0	0	11/68

Abbreviations A = annuloplasty or valvuloplasty AMI = acute myocardial infarction AR = aortic regurgitation AS = aortic stenosis AV = aortic valve MDG = mean diastolic gradient MR = mitral regurgitation MS = mitral stenosis MV = mitral valve NYHA = New York Heart Association OP
Cardiac catheterization not performed but valve obviously stenotic
†Uncorrected by mitral valvuloplasty
‡Patch inserted to widen aortic root

Table II Clinical and necropsy data in patients dying late (> 2 months) after Hufnagel tri leaflet aortic

Necropsy No	Age (years)	Sex	Functional class (NYHA)	No. A V cusps	Preoperative valve lesions				LV-SA PSG (mm.Hg)	LA LV MDG (mm. Hg)	Date AVR (mo/year)	A V size inside diameter (mm.)
					AS	AR	MS	MR				
1 68A 207	74	F	III	3	+	+	0	+	70	0	2/68	16
2 68A 483	51	M	III	3	+	+	+	+	70	5	3/68	18
3 68A 547	59	M	II	3	+	+	0	0	75	0	3/68	?
4 69A 19	76	F	IV	3	+	+	0	0	120	0	1/68	16
5 69A 13	26	M	IV	3	0	+	0	+	0	0	9/67	22
6 69A 577	50	M	II	2	0	+	0	0	38	0	6/68	22
7 68A 453	50	F	III	3	+	+	+	+	60	10	3/67	20
8 70A 419	50	M	III	3	+	+	0	0	38	0	2/69	20
9 70A 509	70	F	IV	3	+	+	0	0	148	0	12/68	16
10 72A 399	53	M	III	2	+	+	0	0	100	0	5/67	18
11 71A 209	36	M	III	3	+	+	0	+	15	0	5/68	22
12 70A 489	43	M	IV	3	+	+	0	+	30	0	10/67	22
13 73A 87	55	M	III	3	+	+	0	0	100	0	5/68	18

Abbreviations See Table I
Replacement of trileaflet aortic prosthesis eight months before death with a disc prosthesis

thetic stenosis from this mechanism uncorrected mitral regurgitation appeared responsible for death in one postoperative bleeding in one and severe intravascular hemolysis of uncertain etiology with renal failure in one

Five of the seven patients who survived more than two days after operation were begun on heparin therapy on the first or second day post operatively and were either on heparin or warfarin sodium at death Three of the four patients who died from prosthetic thrombosis in the early (8 15, and 17 days) postoperative period were on heparin at death and each had received dipyridamole for several days before operation the fourth patient who died two days after operation from a thrombosed prosthetic valve, had not received anticoagulant therapy

Late deaths

The intervals between operation and death in these 13 patients ranged from 2 1 to 58 months (average 22) The one patient dying 2 1 months after valve replacement had aortic regurgitation from a perivalvular leak Of the 12 patients with

valve replacement

A V size inside diameter (mm.)	MV operation	Implantation period (days)	Major cause of death	Status of prosthetic aortic valve						Heart weight (Gm.)	LV scarring (SE) (TM)
				Tears	AR	Thrombus	AS	COO	Emboli		
22	0	1	Bleeding	0	0	0	0	0	0	480	SE
24	0	2	AMI	0	0	+	0	+	0	600	SE
22	A	5	MR†	0	0	0	0	0	0	900	0
16	0	8	AMI	0	0	+	+	+	+	470	SE
16	0	15	AMI	0	0	+	+	+	0	580	0
18	R (disc)	16	Hemolysis	0	0	0	0	0	0	700	SE
18‡	0	17	massive AMI	0	0	+	0	+	+	520	SE

C comm surotomy CHF = co gest hea t f lur COO = onary ost al o lusion F = fem le LA = l ft atrium LV = left ntricl M = m le pe at o PSG = pe k systol gradi nt R = r placem t SA = ystem artery SE = ubendoc rdi l TM = t ansmural

valve replacement

MV Operation	Implantation period (months)	Major cause of death	Status of prosthetic aortic valve						Infection	Peribasilar AR	Heart Weight (Gm.)	LV scarring (SE) (TM)
			Tears	AR	Thrombus	AS	COO	Emboli				
A	2 1	AR	0	0	0	0	0	0	0	+	530	0
C	6	AR	+	+	0	0	0	0	0	0	490	0
O	7 5	AR	+	+	0	0	0	0	0	0	600	SE
O	12	Sepsis	+	+	+	0	0	+	+	+	480	TM
A	15	AR	+	+	0	0	0	0	0	0	850	SE
O	18	AMI	0	0	+	+	+	0	0	0	600	SE
R (disc)	18	AR	+	+	0	0	0	0	0	0	450	SE
O	19	AR	+	+	+	0	0	0	0	0	700	SE
O	23	AMI	0	0	0	0	0	0	0	0	470	TM
O	32	Aortic dissection	+	+	+	0	0	0	0	0	380	SE
A	35	AMI	0	0	+	+	+	+	0	0	690	TM
C	36	AR	+	+	+	0	0	+	0	0	900	SE
O	58	AMI	0	0	+	+	+	+	0	0	700	SE

implantation periods of six months or longer the aortic prosthesis in eight was torn (Figs 3 and 4) severely incompetent and responsible for death (seven patients) or reoperation (one patient) no degeneration of prosthetic material was evident in the other four patients despite long (18 to 58 months [average 29]) implantation periods but three had large thrombi (Fig 5) within the prosthetic sinuses causing obstruction to at least one coronary arterial ostium Histologic examination of the thrombotic material from several patients disclosed it to consist predominantly of fibrin and platelets with only a few erythrocytes Thus it was a so called white thrombus The one patient without prosthetic degeneration or thrombosis died of an acute myocardial infarction from severe coronary atherosclerosis 23 months after valve replacement All patients were discharged from the hospital on warfarin sodium

Renal hemosiderosis the anatomic indicator of intravascular hemolysis (in this case the result of trauma to erythrocytes traversing prosthetic aortic valves[10]) was sought for in the late death cases The kidneys in 11 of the 13 patients dying



Fig 1 View of an intact trileaflet prosthesis from the aortic (*left*) and the ventricular aspect (*right*)

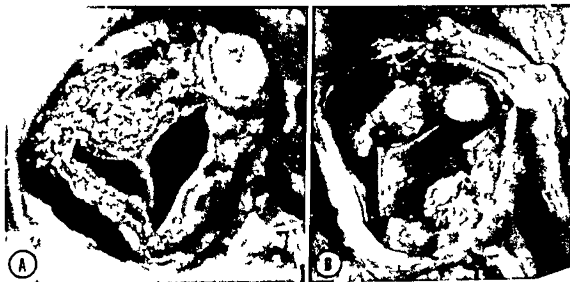


Fig 2 Patient No 4 Table I Prosthesis containing thrombus in each of the three sinuses from a patient dying eight days after valve replacement The thrombus partially blocked the ostium of the left coronary artery *Left* View from aortic aspect about 2 cm above the prosthesis *Right* This view is on a plane corresponding to the cephalad extension of the prosthesis

late were available for study All sections were stained by Prussian blue reaction Four patients had no iron deposits in the kidneys Of the seven who did four had had other prosthetic aortic or mitral valves implanted prior to the Hufnagel prosthesis for periods ranging from 16 days to eight years Two other patients had severe perivalvular leaks and another had a torn degenerated, incompetent prosthesis Thus of seven patients in whom only trileaflet aortic prostheses were used, four had no renal iron deposits while each of the remaining three had prosthetic abnormalities which could account for the hemolysis The pre and late postoperative blood hematocrit values of all seven patients were similar indicating that increased hematopoiesis was able to compensate for the intravascular red cell destruction

Discussion

The trileaflet aortic valve used in the patients described herein consists of three self suspended flexible leaflets made of polypropylene covered with silicone rubber The leaflets are supported from the base and do not attach directly to the aortic wall The base is made of Hepacone (a material which at least in vitro inhibits clotting of blood) except for a small area of Dacron fabric along the suture line (used to stimulate the ingrowth of tissue) Nine to 12 sutures usually are

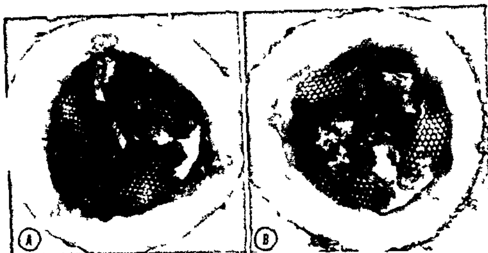


Fig 3 Patient No 5 Table II A severely degenerated prosthesis with extensive tearing of the cusps from above (*left*) from below (*right*)

used for fixation This prosthesis has a central flow orifice similar to the normal valve the cusps are freely pliable open with low pressure and initially were believed to have long flex lives Its central flow characteristic would theoretically make this prosthesis particularly advantageous in patients with small aortas which might impede rigid framed poppets or discs Because it is a central flow valve with smooth surfaced cusps hemolysis does not occur This prosthesis underwent certain changes during its period of clinical application the late model had more shallow sinuses and shorter vertical struts than did the original model.

Despite these theoretical advantages use of this trileaflet aortic prosthesis in its present form has been discontinued because of the frequency of cuspal fracture or fibrin platelet deposition or both Degeneration (tearing) of the prosthetic cusps occurred in eight of 12 patients surviving six months or longer after valve replacement. Cuspal degeneration occurred as early as six months after implantation (in one patient) and not until nearly six years later (in another patient) Degeneration appears to begin by tearing of a cusp from its most cephalad attachment to a vertical strut It is apparently at this point that stress is greatest during valve closure Thrombus formed within one or more of the sinuses of the prosthesis in seven of the 20 patients. All three patients dying late and three of four dying early from prosthetic thrombosis were on anticoagulants Although it is impossible to know whether or not these patients were adequately anticoagulated at all times it appears that the factors of turbulence and difficulties in the control of the equal distribution of stresses in these prostheses are responsible for this frequency of accumulation of thrombi Similar clotting problems obviously also have been encountered with



Fig 4 Same valve as seen in Fig 3 but from below before the valve was excised at necropsy The massive degree of incompetence is apparent



Fig 5 Patient No 13 Table II Prosthetic thrombosis. *Left* as seen from about 1 cm above the sinotubular junction of ascending aorta *Right* as seen on a plane corresponding to the most cephalad extension of the prosthesis Thrombus is present in each of the three sinuses and obstructs the ostium of the right coronary artery

use of other types of prostheses including the caged ball and disc Because of the central flow feature of this prosthesis, research on the use of new forms of flexible leaflet prosthetic cardiac valves is continuing in an effort to overcome the problems of cuspal fracture and thrombosis

Summary

Necropsy observations are described in 20 patients dying between October 1967 and March 1973 after replacement of the aortic valve with a Hufnagel trileaflet prosthesis Seven patients died within two months of operation and 13 between 21 and 58 months (average 22) Four of seven patients dying early had extensive prosthetic thrombus causing obstruction of one coronary arterial ostium in each Of the 12 patients surviving six months or longer after valve replacement death in eight resulted from degeneration (tearing) of the prosthetic cusps causing severe aortic regurgitation in each and from thrombosis of the prostheses in three probably causing prosthetic stenosis and definitely causing narrowing of at least one coronary ostium Thus prosthetic degeneration or thrombosis caused death in 11 of the 12 patients surviving six months or longer In conclusion this trileaflet aortic prosthesis although similar in design to the normal aortic valve, is composed of materials not durable enough to withstand the stresses created by blood flow in this position

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Transient ST-segment elevation with postmyocardial infarction angina prognostic significance*

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The development of new techniques for treating patients with acute myocardial infarction has emphasized the need for more accurate prog nostic assessment of patients presenting with this life threatening pathologic event These new methods of therapy are costly in medical re sources and potentially hazardous to the serious ly ill patient and should be applied only in cases where the outlook for recovery is substantially reduced Objective criteria for assessing prog nosis based on hemodynamic findings have been described,[1,2] but predictive data identifying a pa tient as being at high risk of infarction extension or reinfarction have not, to our knowledge been established. We have encountered a group of pa tients who demonstrated transient ST segment elevation in association with anginal pain during the early postinfarction period and observed a high incidence of reinfarction and death in these patients this report documents our experience in identifying this occurrence describes the course of nine patients with this finding and compares their prognosis with that of other patients having had acute myocardial infarction

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Patient selection and evaluation

During the period June 1971 to August 1972 57 patients with unequivocal acute myocardial infarction were admitted to the David Grant United States Air Force Medical Center The di agnosis of acute myocardial infarction was estab lished by the usual criteria of typical chest pain evolutionary electrocardiographic changes and characteristic serum enzyme elevations Daily 12 lead electrocardiograms and serum enzyme determinations (creatine phosphokinase glu tamic oxaloacetic transaminase and lactic dehydrogenase) were obtained in all cases on ad mission and on the succeeding three days Pa tients were admitted to the cardiac care unit and were under constant observation Special atten tion was given to documentation of episodes of pain or ST segment changes on the electrocar diogram Monitor lead (bipolar right shoulder to Lead V_5 position) electrocardiograms were recorded from a 45 second tape delay at the onset of any episode of pain or on observation of any change in the electrocardiogram pattern Twelve lead electrocardiograms were obtained during many episodes of pain and in all patients experiencing pain during at least one episode Monitor recordings or 12 lead electrocardio grams were then obtained when the chest pain had resolved. Only episodes of pain occurring 24 hours or more after initial infarction were con sidered to represent ischemic episodes distinct from the initial infarction Serum enzyme deter minations were obtained following episodes of pain and for three succeeding days ST segment elevation was considered transient if on resolu tion of the pain the ST segments and T waves re turned to their prepain level and configuration

Table I Clinical course of patients with transient ST segment elevation associated with early postmyocardial infarction angina

Patient No	Age	Sex	Previous infarct	Previous angina	Admitting infarct location	First episode of pain days infarction	Approximate no of episodes of pain	Reinfarction, days after infarction	Course
1	68	M	Ant	Yes	Ant	6	3	33	Died of cardiogenic shock four days after reinfarction
2	68	M	Ant	No	Inf	2	2	37	Died of congestive heart failure 29 days after reinfarction
3	58	M	None	No	Ant	4	3	135	Accelerating angina three months after infarction Died suddenly 135 days after infarction
4	53	M	Inf	Yes	Ant	7	4	12	Asymptomatic after reinfarction
5	48	F	None	No	Ant	2	10	7	Continuing angina with transient ST segment elevation Bypass surgery 33 days after infarction
6	67	F	None	No	Ant	9	10	14	Exertional angina AHA II
7	34	M	None	No	Ant	6	40	14	Exertional angina AHA III
8	70	M	None	Yes	Ant	2	15	None	Exertional angina AHA III
9	75	M	Ant	No	Ant	3	2	None	Asymptomatic after discharge

Ant anterior Inf inferior * see text.

subsequent evolutionary changes did not interrupt the established infarct evolution on the electrocardiogram and serial serum enzyme determinations did not show a postpain elevation The diagnosis of reinfarction was based on occurrence of chest pain with a significant increase in serum enzymes further loss of R waves deepening of Q waves or reinversion of T waves that had become upright The minimum period of hospitalization was 21 days from the date of infarction which in most cases was manifest the day of admission Following discharge the patient s care was provided by one of the authors and average follow up period was twelve months

Results

On the basis of their clinical course and electrocardiographic findings, patients with acute myocardial infarction admitted during the study period were included in one of these groups (1) patients with episodes of anginal pain occurring more than 24 hours after initial infarction, associated with transient ST segment elevation (2) patients with anginal pain occurring more than 24 hours after infarction without ST segment changes or with ST segment depression and (3) patients who had no anginal pain during their postinfarction hospital course

The clinical course of the nine patients in Group 1 is outlined in Table I Each of the nine patients had transient ST segment elevation in association with anginal chest pain recorded on at least two separate occasions (Figs. 1 and 2) The electrocardiographic localization of the transient ST segment elevation was closely related to the area of initial infarction, occurring in a region different from that in which the initial infarction occurred in only one case In the six patients who sustained reinfarction with electrocardiographic confirmation five occurred in the same region as did the transient ST segment elevation the only exception (No 4) reinfarcted in the area of his initial anterior infarction while his transient ST segment elevation had occurred in the inferior leads of the electrocardiogram

Three of the nine patients in Group 1 died Patients No 1 and No 2 both had mild and readily compensated heart failure after their admitting

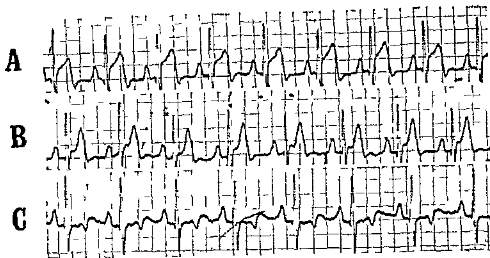


Fig 1 Transient ST segment elevation associated with postinfarction angina demonstrated on the monitor lead electrocardiogram *A* is at onset of chest pain *B* is three minutes after administration of 0 6 mg of nitroglycerin sublingually with pain decreasing *C* is five minutes after nitroglycerin with pain resolved, and is the same as the patient s monitor electrocardiogram prior to the onset of pain.

infarction but developed severe low output failure after reinfarction progressing to cardiogenic shock and death Postmortem examination in both patients demonstrated severe obstructive coronary atherosclerosis in all three major coronary arteries Patient No 3 was rehospitalized four months after his initial infarction because of accelerating angina Five days after coronary angiography (for results, see below) while awaiting surgery he developed severe chest pain and collapsed Resuscitative measures were unsuccessful Although permission for postmortem examination was not given it was presumed that he had a myocardial ischemic episode as his terminal event

Three Group 1 patients had coronary angiography Two patients (No 5 and No 7) showed total obstruction of the left anterior descending coronary artery near its origin with retrograde flow to the artery beyond the obstruction from right coronary artery collaterals Both of these patients however demonstrated high grade right coronary artery obstructions proximal to the origin of the collateral vessels Patient No 7 was found to have distal as well as proximal disease and was unsuitable for revascularization surgery Patient No 5 had angiography early after her reinfarction because she continued to have resting chest pain with transient ST segment elevation Aortocoronary saphenous vein bypass surgery was successfully accomplished 33 days after her initial infarction Patient No 3 demonstrated a high grade but not total proximal obstruction of the left anterior descending artery with angiographic antegrade filling of the distal vessel which was markedly delayed and with prolonged washout. A high grade obstruction was also present in the right coronary artery in this patient but there was no evidence for collateral blood flow to the distal left anterior descending artery

Eight of the Group 1 patients were treated with heparin anticoagulation and six were treated with frequently administered sublingual isosorbide dinitrate Propranolol was not utilized in any patient

Group 2 is comprised of 17 patients who had anginal pain in the early postmyocardial infarction period, occurring at rest, and associated with either ST segment depression or no change in the ST segment Two of these patients had a reinfarction one four days and one five days after their initial myocardial infarction but survived Two additional patients died both of progressively severe heart failure and within one month of their initial infarction No further infarctions or deaths occurred in this group over an average follow up period of 12 months

Of the 31 patients in Group 3 who had no angina in the early postmyocardial infarction period, two reinfarctions occurred one six days after initial infarction and one five months after initial infarction The patient who reinfarcted at day six did not have preceding angina and the

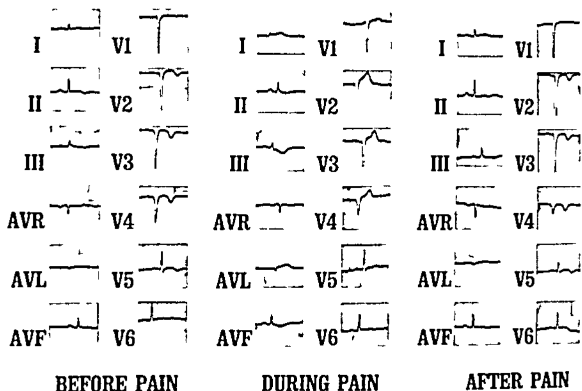


Fig 2 Twelve lead electrocardiogram before during and after complete resolution of anginal pain nine days after the patient's admitting infarction Subsequent electrocardiograms showed continuing evolutionary changes of the admitting anterior infarction and there were no serum enzyme elevations.

first episode of pain after his initial infarction was associated with enzymatic and electrocardiographic evidence of reinfarction The patient who reinfarcted four and a half months after initial infarction did not have chest pain during the recovery period from his initial infarction but did have exercise induced angina three to four weeks prior to his second infarction Two patients in this group died one three and a half weeks and the other four weeks after initial infarction One developed an arrhythmia which led to asystole while the second was unexpectedly found dead in bed

When the total number of reinfarctions and deaths in these three groups of patients are compared there is a statistically significant ($p < 0.05$ by Chi square analysis) increased incidence of cardiac events (reinfarction and/or death) in the patients who demonstrated transient ST segment elevation with postmyocardial infarction angina when compared with the other two groups of patients either singly or combined When the incidence of reinfarction and death in patients with angina but without ST segment elevation (group 2) and those without angina (Group 3) is compared there is no statistically significant difference

Discussion

Transient ST segment elevation with anginal pain was described by Prinzmetal and coworkers[3] in 1960 as one characteristic of a syndrome he called variant angina pectoris It was found that a single high grade proximal coronary artery obstruction was present in many cases of variant angina [4,5] and it was postulated that coronary artery spasm might be superimposed on such a lesion leading to profound but transient ischemia in the region of the involved vascular bed causing the characteristic electrocardiographic changes Coronary angiographic studies in a few patients have recently confirmed the fact that severe coronary artery spasm can indeed be a cause of the syndrome of variant angina pectoris [6,7] even in patients without demonstrated fixed obstructive lesions ST segment elevation has also been described in association with exercise induced angina pectoris [8,9] In contrast to the anatomic findings in variant angina pectoris ST segment elevation with exercise occurs almost exclusively in patients with severe diffuse coronary artery disease

We have described in this report another clinical setting that of the early postmyocardial infarction period in which transient myocardial

ischemia is manifested electrocardiographically by ST segment elevation Postmortem examination or coronary angiography obtained in five of our nine patients showed severe and widespread coronary artery obstructive disease and angiographically markedly compromised blood flow to the area of myocardium demonstrating the ST segment elevation It is likely that this compromised perfusion to the region of infarction was adequate to maintain some tissue viability within or surrounding the infarcted tissue but if any factor led either to an increase in oxygen demand or to a reduction in the already compromised blood flow profound ischemia of the remaining viable muscle ensued. It is probable that the transient ST segment elevation observed is a sign of the profound ischemia most likely transmural in extent a concept which is supported by experimental data as well as the clinical correlations already cited.[10]

Because of the poor prognosis in this group of patients as compared with other patients with acute myocardial infarction it seems appropriate to consider more aggressive therapeutic measures Anticoagulation and nitrite administration had no apparent beneficial effect on our patients High dose beta adrenergic blockade has been reported to be useful in the treatment of variant angina pectoris[11] but one is reluctant to use large doses of a negative inotropic agent in the immediate postinfarction period. Surgical revascularization may prove to be the most beneficial long term therapeutic measure but the risk of surgery soon after a myocardial infarction is increased[12] and reperfusion of a recently infarcted area may even cause an increase in the size of infarction[13,14] These patients may be an appropriate group in whom to consider the therapeutic reduction of ventricular afterload and augmentation of diastolic perfusion pressure either by pharmacologic means[15] by mechanical devices[16] or by a combination of these therapeutic innovations[17,18] These techniques may allow a period of stabilization and healing which will reduce the risk of angiography and increase the chance of surgical success in these seriously ill patients if surgery is ultimately deemed necessary

Summary

Fifty seven patients with acute myocardial infarction were observed for early postmyocardial infarction angina and associated transient ST segment changes Nine patients had postinfarction angina with transient ST segment elevation (Group 1) seventeen patients had postinfarction angina with ST segment depression or no ST segment changes (Group 2) and 31 patients had no postinfarction angina (Group 3) The patients in Group 1 had a statistically significant increased incidence of early reinfarction and death when compared with the other two groups singly or combined. There was no significant difference in the incidence of reinfarction and death when Group 2 is compared with Group 3 Patients with transient ST segment elevation associated with early postmyocardial infarction angina may be an appropriate group in whom to consider newer more aggressive modes of postinfarction management

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Double chamber right ventricle experience with 17 cases

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Sir Arthur Keith focused attention on obstructive muscle bands within the right ventricular cavity in his Hunterian lecture of 1909[1] Interest in these lesions was revived in 1962 by Lucas and associates[2] who pointed out the association of anomalous muscle bundles of the right ventricle with other forms of congenital heart disease and stressed the importance of their recognition during intracardiac surgical procedures

A plethora of reports[3-11] have since defined the double chamber right ventricle (DCRV) as created by one or more muscle bundles traversing the sinus portion of the right ventricle (RV) well beneath the infundibulum passing forward from the midportion of the crista supraventricularis to the anterior wall at the base of the anterior papillary muscle and creating varying degrees of obstruction to blood flow

Certain questions concerning DCRV remain unresolved What is its embryonic origin in relationship to the genesis of other heart anomalies? Can DCRV be suspected clinically in the absence of angiography? What is the natural history of this anomaly and does it cause progressive right ventricular obstruction?

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In an attempt to answer these questions we have reviewed our experience with 17 consecutive patients with DCRV admitted to the Children s Hospital Medical Center Boston during the period 1966 through 1972 (Table I)

Materials and methods

The 17 patients reviewed satisfied the following laboratory criteria (1) a pressure gradient recorded between right ventricular sinus and subpulmonary area (2) right ventricular angiography revealing an obstructive filling defect below the infundibulum that demarcated a well defined coarsely trabeculated chamber both proximal and distal to the site of obstruction and (3) absence of infundibular hypoplasia

The clinical profile catheterization studies and surgical experience of the patients were reviewed Postmortem specimens of the three children who died were examined and compared to normal heart specimens

Results

Clinical picture Gestational delivery and neonatal histories were unremarkable Two of the 17 cases were one of twins with no indication of congenital heart disease in the sibling Three had associated extracardiac anomalies (cleft palate unilateral renal hypoplasia and polysplenia syndrome)

Of 16 patients in whom information was available 10 had a heart murmur first detected in the newborn nursery In the remaining six murmurs were initially heard within six weeks of age Clinical diagnoses prior to cardiac catheterization were ventricular septal defect (VSD) in thirteen valvular pulmonary stenosis in two and

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Center Boston over a six year period

Right ventricular inflow pressure (mm Hg)	VSD (Qp/Qs)	Associated lesions	Symptoms	Chest x ray cardiac enlargement +++ = severe	Electrocardiogram QRS Axis	RVH	LVH	Surgery
165/–	0	SubAs	+	+	+75	+	0	+
96/–	Tiny	0	0	0	+100	+	0	+
110/–	0	0	0	0	+105	+	0	+
93 11	1 2	0	0	+	+70	+	+	
102/–	<1 0	PFO	+	0	+145	+0	+	
75/5		0	+	0	+85	+	0	+
120/–	1 2							
85/6	2 0	IS PFO	0	++	+120	+	0	+
90/8	3 0	PS PFO						
78/–	3 1	0	0	+	+120	+	0	0
77/6	1 6	PPS	0	+	+30	++	0	
87/3		0	0	0	+80	+	0	+
41/12	1 9							
42/5	2 0	0	0	+	+60	0	0	0
36/3	2 4							
62/–	1 8	PFO	0	+	+10	0	0	0
62/7	7 0	ASD	+	++	+110	+	+	
55/9	2 0		+	++	100	+	+	
82/3	1 1		0	0	+90	0	0	+
41/2	1 7	SubAs	+	+++	+20	0	+	+
80/9	Tiny	TAPVR ASD	+	++	+180	+	0	0
60/6	1 4	0	0	0	+85	0	0	0
49/6	Tiny	0	+	+	+75	+	0	0

PPS = peripheral pulmonary stenosis PFO patent foramen ovale ASD = atrial septal defect VSD = ventricular septal defect and TAPVR –

sternal border in every case The murmur heard at the same location was described in all patients as coarse long and loud

Group II Two patients presented with tetralogy of Fallot physiology and right to-left shunting through a VSD from the inflow right ventricular chamber In one of the patients a history of cyanosis dyspnea and possible spells along with clubbing and auscultatory findings typical of tetralogy of Fallot created a clinical picture indistinguishable from this lesion. The second patient had mild cyanosis

Group III Seven patients had moderate sized VSDs and exclusive left to right shunting All but one were asymptomatic A systolic ejection click was audible in the one patient with associated valvular pulmonary stenosis The second heart sound was of normal intensity with usual inspiratory splitting in five patients widely split and fixed in one patient with an associated atrial defect and obscured by the murmur in the seventh patient One subject included in this category demonstrated a clear progression from congestive heart failure with pulmonary artery hypertension in infancy to spontaneous decrease in the size of the VSD and the development of severe right ventricular obstruction in childhood (Table I WS)

Group IV In two patients with a trivial VSD and mild right ventricular obstruction and in the patients with severe subaortic obstruction (DS) and asplenia syndrome (DC) DCRV was hemodynamically unimportant The latter two patients suffered from profound congestive heart failure and exhibited findings typical of their more significant associated lesions

Laboratory data

Electrocardiograms The electrocardiogram was normal in only two patients The patients in Group II showed severe right ventricular hypertrophy Seven patients all in Groups I and III displayed right ventricular hypertrophy of a

Table I Seventeen patients with double chamber right ventricle admitted to Children's Hospital Medical

	Patient	Sex	Age at catheterization (years)	Pulmonary artery pressure (mm. Hg)	Right ventricular outflow pressure (mm. Hg)
Group I	JZ	M	3	18/10	100/–
	MR	M	11	19/4	20/–
	LK	F	13	26/9	26/–
	AT	M	5	21/9	35/9
Group II	HG	M	4	15/5	32/–
	CP	M	8	18/5	18/5
			9	25/10	35/8
Group III	JM	M	7	23/8	37/5
			15	20/13	35/–
	RV	M	3	19/–	50/–
	TC	M	4	24/6	21/5
	AV	F	5	20/6	20/2
			6	32/11	–
	CA	F	10	17/5	–
			20	20/11	–
	RB	M	7	20/4	2[illegible]/–
	WS	F	3/12	60/24	–
			1	38/9	–
			5 3/12	20/6	23/3
Group IV	DS	M	5	20/10	27/4
	DC	M	3/12	26/9	–
	JS	M	13	22/10	24/8
	EJ	M	8	23/8	26/5

Abbreviations RVH = right ventricular hypertrophy LVH = left ventricular hypertrophy PS = pulmonary stenosis SubAs = subaortic stenosis total anomalous pulmonary venous return and Qp/Qs = pulmonary/systemic flow ratio

tetralogy of Fallot in two The diagnosis of DCRV was not made prior to catheterization in any of the patients

Associated cardiac abnormalities Of the 17 cases 16 had associated cardiac lesions A VSD was present in 15 cases There was no relationship between the size of the VSD (as measured by pulmonary to systemic flow ratio) and the measured right ventricular gradient Discrete subaortic stenosis was found in two patients and valvular pulmonary stenosis peripheral pulmonary stenosis, atrial septal defect secundum and total anomalous pulmonary venous connection (with polysplenia syndrome) were present in one patient each

Physiologic classification DCRV patients can be divided into four hemodynamic categories depending on the degree of right ventricular obstruction and size of the VSD Group I pulmonary stenosis with intact ventricular septum physiology Group II tetralogy of Fallot physiology Group III large VSD with left to right shunt and Group IV DCRV as an associated anomaly which is hemodynamically insignificant This classification encompasses the spectrum of physiologic abnormalities encountered in patients with DCRV and explains the variability in clinical features and laboratory findings (Table I)

Group I Four patients demonstrated severe right ventricular obstruction with either a tiny VSD or intact ventricular septum All were without symptoms with the exception of the single patient with suprasystemic inflow right ventricular pressure who was well until the age of two years when circumoral cyanosis and increased ease of fatigue were noted On auscultation the second sound was obscured by the murmur in two cases narrowly split with a diminished pulmonary component in another case and felt to be normal in one case

A thrill was detected at the mid to lower left

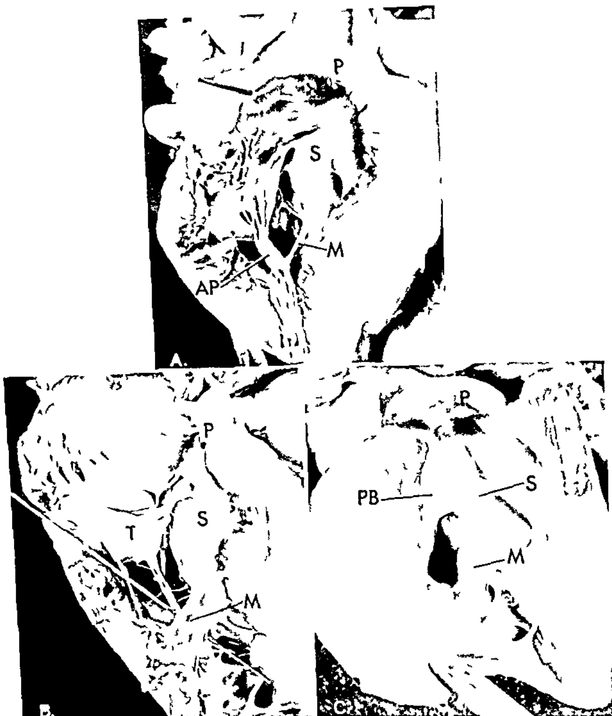


Fig 2 Right ventricular outflow tract anatomy of three separate hearts demonstrating progressive obstruction to blood flow with increasing height of moderator band take off from septal band. *A*, normal heart with usual moderator band (M) arising low off the septal band (S) and inserting at the base of the anterior papillary muscle (AP) Infundibulum and pulmonary valve (P) are normal *B* normal heart with elevated but probably non obstructive take-off of moderator band representing a forme fruste double chamber right ventricle Chordae tendineae to leaflets of the tricuspid valve (T) arise from the inferior portion of the band. A small communication beneath the moderator band connecting inflow and outflow regions of the right ventricular sinus is demonstrated. *C*, patient DC with thick obstructive moderator band originating high from the septal band near the crista supraventricularis and creating a 54 mm intrachamber gradient The parietal band (PB) is normally located but hypertrophied. The anterior papillary muscle tricuspid valve and VSD in the inflow chamber are obscured from view



Fig 1 Right ventricular cineangiogram of patient DC The catheter reaches the right heart via the azygos venous system in this child with polysplenia syndrome *A* anteroposterior projection demonstrating typical double chamber right ventricle muscular filling defect (arrows) dividing the ventricular sinus and obstructing outflow *B* lateral view revealing tongue like mass protruding from the crista supraventricularis inferiorly toward the anterior free wall Postmortem specimen of this heart is shown in fig 2 *C*

more moderate degree with an rsR pattern in Leads V_4R and V_1 a deep S in Lead V_6 and prominent R in Lead aV_R Five of the 17 patients demonstrated tracings suggested to be typical of DCRV[7 10] inconspicuous R in Lead aV_R prominent R with little or no S in Lead V_4R and normal voltages in Lead V_1 and the remaining precordial leads These patients were present in each of Groups I III and IV

Chest x ray The plain chest roentgenogram was of little aid in the diagnosis of DCRV Seven examinations at the time of last cardiac catheterization were normal and only three patients demonstrated significant cardiomegaly In the remainder of the patients mild cardiac enlargement with or without a small increase in pulmonary blood flow was described In none of the patients was the main pulmonary artery felt to be prominent

Phonocardiogram and vectorcardiogram Phonocardiograms were performed on only two patients with moderate sized VSD s and gradients of 55 and 16 mm Hg, both showed a widely split second sound and diminished intensity of pulmonary valve closure Vectorcardiograms in eight patients reflected electrocardiogram findings and were of no particular diagnostic benefit

Cardiac catheterization In eight patients the inflow right ventricular chamber was at systemic pressure levels and in one case pressures were suprasystemic The gradient imposed by the right ventricular muscle band ranged from 14 to 147 mm None of the patients had pulmonary hypertension at final preoperative catheterization

Pressure tracings were not consistently reliable in establishing the levels of right ventricular obstruction In one case (JZ) a separate 82 mm gradient was recorded across the pulmonary valve which was found to be normal at operation The catheter flipped from the pulmonary artery directly to the inflow high pressure right ventricular chamber in two cases

Right ventricular angiograms revealed obstruction by a diagonal muscle bundle dividing the ventricular sinus into a proximal inflow chamber containing the tricuspid valve and outflow coarsely trabeculated chamber including an apical recess The obstructing band appeared single in all cases it was best seen in the anteroposterior projection early during the injection of contrast material, and during ventricular systole On lateral view the muscle bundle frequently appeared as a tongue like mass arching anteriorly and inferiorly to insert approximately 2/3 down the anterior right ventricular wall (Fig 1) The subpulmonary conus was well developed in all patients

Natural history Three patients underwent repeat cardiac catheterization after a 5 8 , and 10 year interval with insignificant changes in gradient of +15 +7 and −9 mm Hg, respec

that depending on the degree of right ventricular obstruction and significance of associated anomalies DCRV may mimic a wide spectrum of congenital heart disease Thus while the presence of DCRV may be suspected from certain clinical features[6,10] (loud, coarse murmur obscuring the second heart sound isolated electrocardiogram signs of right ventricular hypertrophy in Lead V_4R) this lesion cannot be faithfully diagnosed without cardiac catheterization and selective right ventricular angiography

Furthermore the presence of a VSD aortic outflow obstruction or other cardiac anomaly should be carefully sought at the time of catheterization or surgery in DCRV patients That even with such precaution defects may be over looked is illustrated by our patient with a moderate sized VSD that went undetected at both initial catheterization and during the operation

Associated cardiac lesions most commonly VSD have been reported in 80 per cent of patients with DCRV[6] and the incidence was even higher in our group of patients (88 per cent) The rarity of isolated DCRV leads us to suspect that such cases may represent either improperly diagnosed infundibular stenosis or DCRV in which spontaneous closure of a VSD has occurred prior to the time of catheterization

Can right ventricular obstruction progress with time? Of four patients in our series who had serial catheterizations three showed no significant change in gradient and one a definite progression with the development of a large gradient Hartmann Goldring and Carlsson[4] and Forster and Humphries[8] have also presented data indicating that an increase in obstruction may occur

In the absence of adequate data describing the natural history of DCRV indications for surgical intervention are not presently clear Because progressive dyspnea cyanosis and right sided heart failure occur in patients with severe valvular pulmonary stenosis[16] we advise operation on all children with DCRV provided pressures in the proximal chamber approach systemic levels

The embryogenic mechanism of the DCRV VSD relationship is unclear but improper expansion of the bulboventricular junction may result in incomplete fusion of the bulbar and endocardial cushion elements that normally close the superior portion of the ventricular septum

Based on his studies of comparative anatomy

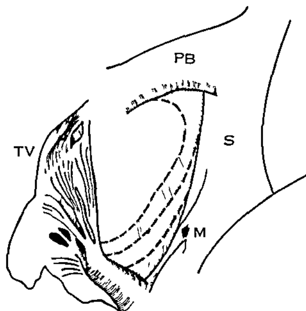


Fig 3 Schematic diagram of the right ventricular cavity demonstrating progressive elevation of moderator band (M) take off from the septal band (S) producing a reorientation of the former structure which compromises right ventricular blood flow TV = tricuspid valve PB = parietal band.

Keith[1] viewed right ventricular subdivision and obstruction as representing arrested incorporation of the primitive bulbus cordis into the right ventricular body According to this concept all portions of the right ventricular cavity above the moderator band as well as the most distal segment of the left ventricular outflow tract are of bulbar *origin*[17] More contemporary authors[2] have disclaimed the importance of the moderator band attributing the formation of DCRV to the abnormal persistence of early myocardial cells or fetal trabeculations in the primitive ventricle chamber[8,11] Goor[18] stated that the septal and moderator bands of the right ventricle are indistinct anatomical structures with no developmental significance

Contention that the obstructing muscle tissue in DCRV is not a moderator band has been based on the observation that the latter normally arises from the inferior portion of the septal band and crosses the apical portion of the right ventricle to the base of the anterior papillary muscle without compromising blood flow[2] We agree with Van Praagh (personal communication) that the postmortem observations strongly suggest that right ventricular obstruction in patients with DCRV results from an elevated origin of a hypertrophied moderator band from the septal

tively There was also no significant change in the left to right shunt through the VSD In one other patient however, three catheterization studies over a five year period clearly demonstrated the development of progressive obstruction from an anomalous muscle bundle and spontaneous diminution in size of the VSD

Surgery Seven patients have undergone surgical resection of obstructing right ventricular muscle bands on cardiopulmonary bypass and two others with DCRV have been operated upon for associated cardiac lesions The latter patients (DS and JM) both suffered intraoperative deaths DS developed an arrhythmia during induction of anesthesia and JM died following injury to the right coronary artery incurred because of extensive scarring from a previous exploratory thoracotomy The seven patients with muscle band excision had an uneventful postoperative course and are asymptomatic an average of 32 months after surgery

Four patients had both muscle band resection and VSD patch closure in three cases the septal defect was proximal to the right ventricular obstruction An associated VSD in a fifth child escaped recognition at preoperative cardiac catheterization and again by direct observation of the ventricular septum at surgery Postoperative congestive heart failure prompted recatheterization disclosing a VSD with a Qp/Qs of 1 9/1 0 The postoperative electrocardiogram in all but one of the patients with band resection demonstrated right axis deviation and right bundle branch block

Surgery was not performed in eight of the 17 patients One of these (DC) died due to complications associated with the polysplenia syndrome

Pathology Comparison of the right ventricular anatomy of three postmortem DCRV specimens with that of a series of normal hearts revealed that a continuum of positions exists from which the moderator band arises from the septal band and that a progressively higher and more posteromedial take off from the septal band created increasing obstruction to right ventricular flow (Fig 2)

Patient DC A moderator band arose high from the septal band near the crista supraventricularis and partitioned the right ventricle as a solid muscular ridge with a single aperture above the band connecting the inflow and outflow portions of the ventricular sinus Although equal in size to the full diameter of the tricuspid valve annulus the obstructive nature of this orifice during life was evidenced by prominent endocardial thickening (jet lesions) best seen on its inflow rim as well as by the 54 mm gradient recorded at cardiac catheterization This inconsistency may be explained by surmising that ventricular systole causes a substantial reduction of orifice size and that the gradient across the obstruction may have been exaggerated by the large flow of the left to right shunt (TAPVR) in this patient

The small membranous VSD entered the high pressure right ventricular chamber There was no pulmonary infundibular stenosis, and the parietal band was normally located The parietal band was especially prominent in forming the 'roof' of the obstructing orifice and may have contributed significantly to the DCRV gradient.

Patient JM A displaced moderator band spanned the right ventricular cavity forming a narrow channel both above and below the band. Fenestrated rather than solid, the obstructing muscle was lined by an impressive degree of endocardial thickening The VSD was large and retrocristal and communicated with the right ventricular inflow chamber

Patient DS The solid obstructing moderator band resembled that of DC The single communicating ostium was considerably smaller than the orifice of the tricuspid valve and was surrounded by jet lesions suggesting a significant restriction of flow While a trivial 14 mm gradient was recorded at catheterization, the distance from the right ventricular outflow tract to the tricuspid valve in these patients is very short and the high pressure inflow chamber may have been missed on the catheter withdrawal tracing in this case The VSD was high small, and membranous entering the proximal right ventricular chamber

Discussion

DCRV as a clinical and anatomic entity should be separated from other forms of right ventricular obstruction Infundibular fibromuscular stenosis [12] reactive cristal hypertrophy [13] and infundibular hypoplasia (tetralogy of Fallot)[14] all create subpulmonary pressure gradients but may be distinguished from DCRV by the lack of a distal coarsely trabeculated right ventricular chamber on selective angiograms

Our experience confirms earlier reports[3 9 15]

Experimental and laboratory reports

Sequence of repolarization on the ventricular surface in the dog

Gernot Autenrieth M D *
Borys Surawicz M D
Chien Suu Kuo M D **
Lexington, Ky

The morphology of the T wave depends on the sequence of ventricular repolarization This sequence is determined by the shapes and durations of the individual ventricular action potentials Our knowledge of the normal sequence of ventricular repolarization stems almost exclusively from the measurements of local refractory periods in the dog heart [1 3]

It has been assumed that the functional refractory periods reflect the durations of action potentials in the ventricular myocardium [3] This assumption is justified when all ventricular action potentials (1) exhibit the same relation between the recovery of excitability and the membrane potential (2) have the same slope of phase 3 and (3) differ from each other in duration only because of different durations of phase 2 If these conditions are fulfilled and if the shape of the transmembrane action potential is known the T wave morphology can be derived from the sequence of the functional refractory periods [4]

Successful recordings of transmembrane action potentials (TAP) with capillary microelectrodes from a heart in situ is technically very difficult It is less difficult if the recording of monophasic action potentials is done (MAP) using suction electrodes It has been shown that the shape and duration of the MAP is the same as those of the TAP [5] We have applied suction electrodes to map out the sequence of repolarization on the surface of the dog ventricle The purpose of this paper is to report this sequence in relation to the T wave and to the ventricular gradient (VG)

Methods

Studies were done on 21 mongrel dogs weighing 13 5 to 25 kilograms and anesthetized with sodium pentobarbital (30 mg per kilogram) administered intravenously The chest was opened by a midsternal incision and the animals were ventilated with a respirator (Harvard Apparatus) To gain access to the posterior wall of the heart an additional lateral incision was made in several dogs To slow the heart rate we performed bilateral upper thoracic sympathectomy removing the paravertebral sympathetic chain cephalad to the fifth thoracic vertebra including the stellate ganglia The heart was suspended in a pericardial cradle and a bipolar Grass E2B platinum electrode was attached to the right atrial appendage Another bipolar electrode was sutured to the right ventricle The atria were paced (Medtronic Pacemaker Model 5800) at the slowest rate required to overdrive the spontaneous rhythm The exposed areas on the cardiac surface were kept as small as possible and were covered with sponges soaked in warm saline These sponges were replaced before each recording The exposed cardiac surface was heated by means of two model L510 explosion proof surgical lamps (12 inches in diameter) (Wilmont Castle Co Rochester N Y) illuminating the site of incision The distance between the heat reflecting lamp surfaces and the heart was adjusted to

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**F rm r U ited States Publ c H alth Cardi ascular T ainee (NIHL Tra ni g Grant N HE-05771 04 05) and Ke tucky H rt Associ t n Rese rch Gr t.

band In the most severe form of DCRV this band originated near the crista supraventricularis, resulting in an orientation quite unlike that of the normal moderator band and producing a significant intra chamber gradient (Fig 3)

This muscular tissue then appears to be "anomalous' only in representing developmental retardation of a normal right ventricular structure supporting Keith's earlier studies The finding of two associated cases of discrete subaortic stenosis in our series strengthens the contention of inadequate bulbar incorporation as an etiologic mechanism

No studies of conduction tissue in DCRV have been reported If this tissue is truly moderator band the muscular partition of DCRV conveys the right common bundle, and its surgical excision may prove hazardous in patients with left anterior hemiblock or other pre existing conduction abnormality [19]

Summary

Double chamber right ventricle (DCRV) is a distinct anatomic entity created by a high take off of the moderator band resulting in obstruction to flow within the sinus portion of the right ventricle Frequently associated with a VSD DCRV exhibits no typical clinical findings and thus cardiac catheterization and angiography are requisite for its identification Proper pre surgical diagnosis and full knowledge of associated cardiac lesions should provide a minimal operative risk and excellent prognosis for patients with DCRV

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Table I Activation time (AT) of monophasic action potentials (MAP s) on the ventricular surface

Region	*No of Dogs*	*No of MAP s*	*AT Average ± S D in milliseconds*	*Significant differences between regions*	*AT Average ± S D as per cent of QRS duration*	*Significant differences between regions*
Posterior base (1)	17	44	29 1 ± 6 4	2† 3† 4	57 5 ± 11 8	2 3 4 5†
Posterior middle (2)	21	50	25 5 ± 5 5	1† 3†	49 2 ± 10 1	1 3 4‡
Apex (3)	18	35	21 6 ± 6 7	1† 2† 5‡	41 5 ± 12 6	1 2 5
Anterior middle (4)	11	14	20 6 ± 6 1	1 5‡	41 6 ± 13 0	1 2‡ 5‡
Anterior base (5)	16	35	25 9 ± 7 9	3‡ 4‡	50 9 ± 15.5	1‡ 3 4‡

p < 0 001
†p < 0 01
‡p < 0 05

val from the beginning of the QRS complex to the onset of the steep upstroke of the MAP (MAP_i) and the MAP duration as the interval from the MAP to the end of MAP (MAP) The latter point represented the intersection of the baseline with the tangent to the steepest part of the MAP downstroke (Fig 1)[7] The interval between the end of MAP and the end of T wave (MAP − T) was assigned a positive sign when MAP occurred earlier than T

The accuracy of the measured intervals was within 5 msec This was determined by repeated measurements made by the same observer and by independent measurements made by two different observers

We divided the surface of the heart into sixteen areas of approximately equal size and attempted to explore each area in each dog However this was not feasible and we obtained acceptable records only from five to 14 areas per dog Since the numbers of records obtained from each of the small areas were not sufficient to analyze the results statistically we grouped the data from several neighboring small areas We combined the small areas into the following five larger areas apex (A) anterior middle (AM) posterior middle (PM) anterior base (AB) and posterior base (PB) The landmarks separating anterior and posterior surfaces consisted of the obtuse cardiac margin on the left side and the acute cardiac margin on the right side of the heart The apical area was bound superiorly by a circular line perpendicular to the long axis drawn at a distance equal to one fourth of the long axis The line separating the middle area from the base bisected the remaining three fourths of the long axis. Standard statistical tests

Table II Differences between monophasic action potential durations in 73 simultaneously recorded pairs

	No of dogs	*No of pairs*	*Differences in milliseconds*	
			Range	*Average ± S D*
PB vs PM	5	11	+ 9 to −12	0 0 ± 7 2
PB vs A	3	6	− 4 to −27	−13 3 ± 8 1
PB vs AB	4	7	−28 to + 4	−10 7 ± 10 5
PM vs A	6	14	+23 to −35	− 8 7 ± 14 2
PB vs AB	3	4	− 2 to −12	− 8 5 ± 4 4
A vs AB	6	8	+13 to − 3	+ 6 3 ± 5 5
AB vs AM	7	23	+18 to − 6	+ 0 6 ± 5 6

were used to evaluate the significance of the results

Results

T wave In agreement with previous studies we found that the bilateral sympathectomy had only a slight and inconsistent effect on ventricular repolarization[8] The shape of the T wave was similar to that recorded in other studies of anesthetized dogs in the supine position[4,9] The VG in the frontal plane was generally positive i e greater than zero In 86 out of 106 pairs of ventricular complexes recorded simultaneously with acceptable MAP s the VG was positive in both leads In the remaining 20 pairs the VG was positive in one lead and negative in the other lead In all dogs the R wave was the major QRS deflection in Leads II and Y In these leads the T wave was upright with a single or bifid peak in 69 tracings and inverted in 37 tracings

Monophasic action potentials

Activation time The duration of the QRS com

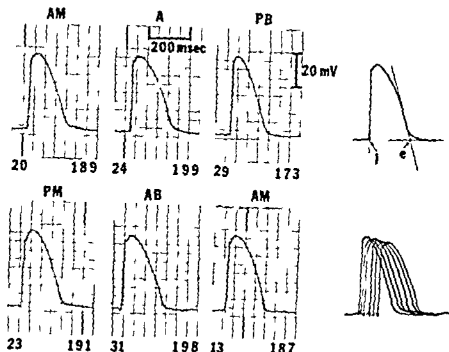


Fig 1 Six monophasic action potentials (MAP) recorded from five different areas in the same dog Abbreviations AM = anterior middle A = apex PB = posterior base PM = posterior middle and AB = anterior base The numbers under each tracing indicate the activation time in milliseconds on the left and the MAP duration in milliseconds on the right. In the right lower corner the MAP s are retraced and placed in a row to illustrate the parallel slopes of repolarization in MAP s of different duration The drawing in the right upper corner illustrates the method of determination of the onset (i) and the end (e) of the MAP The horizontal line represents the baseline The onset of MAP marked by the arrow is the point of intersection between the baseline and the extension of the initial portion of the MAP upstroke (vertical line) The end of MAP marked by the second arrow is the point of intersection between the baseline and the tangent to the steepest portion of repolarization slope (oblique line)

maintain the cardiac surface at a uniform temperature (Tele thermometer Yellow Springs Instrument Company, Inc) ranging in individual experiments from 34° to 37° C

Two electrocardiographic leads and two monophasic action potentials (MAP) from the epicardial surface of the ventricular myocardium were recorded simultaneously with a multichannel direct writing recorder (Hewlett Packard) on a paper moving at 100 mm per second

We recorded standard limb Leads II and Lead aV_L in the initial experiments (12 dogs) and the orthogonal X and Y leads of the system designed for the dog by McFee and Parungao[6] in the subsequent nine dogs The ventricular complexes in Leads II and Y were nearly identical while the complexes in Lead aV_L and Lead X differed from each other We measured Q T interval in both leads and used the value from the lead with the longer interval The ventricular gradient (VG) was determined planimetrically in both leads after enlargement and retracing

MAP s were recorded with bipolar suction electrodes One electrode pole was the tip of a stainless steel wire (diameter 0 07 mm) inserted into the lumen of a polyethelene tube (ID 1 3 mm OD, 1 8 mm) This wire tip touched the epicardium when suction was applied (negative pressure equals 75 mm Hg) The other pole was a cotton thread soaked in saline wound on the outside of the tube at its tip

Ventricular MAP s were acceptable if the course of the repolarization was smooth and the record was not distorted by the QRS and T wave deflections To test the influence of the ventricular electrocardiogram (ECG) complex on the MAP we compared the tracings recorded during atrial pacing with those recorded during ventricular pacing The MAP s were acceptable if (1) both atrial and ventricular pacing produced identical tracings (2) the MAP amplitude exceeded 25 mV and (3) ten or more consecutive MAP s were identical In some experiments only one of the two simultaneously recorded MAP s was acceptable

The activation time was measured as the inter

Table III Duration of the monophasic action potentials (MAP) expressed in per cent of the longest MAP in each dog

Region	*No of Dogs*	*No of MAP s*	*Range*		*Average ± S D*
Posterior base	17	44	81 2	100 0	90 1 ± 4
Posterior middle	21	50	82 4	100 0	93 3 ± 4
Apex	18	35	87 5	100 0	96 2 + 4
Anterior middle	11	14	88 1	99 1	94 5 ± 3
Anterior base	16	35	89 0	100 0	96 0 + 3

Table IV Statistical significance of the regional differences between the durations of monophasic action potentials (MAP)

Regions	*Pairs of MAP s P value*	*Single MAP s† P value*
PB vs PM	NS	⟨0 001
PB vs A	⟨0 01	⟨0 001
PB vs AM	–	⟨0 001
PB vs AB	⟨0 05	⟨0 001
PM vs A	⟨0 05	⟨0 01
PM vs AM	–	⟨0 01
A vs AB	⟨0 05	NS
A vs AM	–	NS
AB vs AM	NS	NS
PM vs AB	⟨0 05	⟨0 01

Tabl II
†T ble III



Fig 3 Distribution of the intervals between the end of the monophasic action potential (MAP) and the end of the T wave in 178 tracings (see text)

Table V Relation between the duration of monophasic action potential (MAP) expressed in per cent of longest MAP in each dog and the activation time (AT) on ventricular surface

Group	*AT (msec.)*	*No of dogs*	*No of AP s*	*Duration average ± S D in per cent*	*Significant differences between groups*
I	8 20	14	46	95 1 ± 3 4	III
II	21 30	17	97	94 4 ± 4 5	III†
III	⟩31	21	41	92 5 ± 4 7	I II†

p⟨0 01
†p⟨0 0

AP duration on the ventricular surface and the VG The MAP s were generally shorter on the posterior than on the anterior surface of the ventricles and shorter at the base than at the apex The latter finding is opposite to the order of repolarization suggested by Haas and co workers[12] and several other older studies[14] However our results are in agreement with a recent study of Burgess and co workers[3] where the refractory records were longer at the apex than at the base by 5 to 20 msec in seven experiments

Our study suggests that progressive MAP shortening in progressively later activated areas is determined by the time of activation rather than by the site of activation This distribution of the recovery properties confirms the results of Burgess and co workers[3] and supports the validity of the concept of the ventricular gradient (VG) The relation of MAP duration on the ventricular surface in this study agrees with the direction of VG in our ECG s

Dispersion of repolarization Van Dam and Durrer[2] *found that in the innermost layers the refractory periods were* sometimes approximately 15 msec longer than the middle and subepicardial layers In our study the average maximum dispersion of MAP duration was 22 ± 9 msec This is similar to the MAP dispersion on the surface of the isolated cat heart which averaged 25 msec[15] These two studies suggest that the dispersion of AP duration on the entire surface exceeds the transmural differences of refractory periods

Some indication of the approximate maximum dispersion of repolarization in an individual dog can be obtained from the relation between the timing of the T wave apex and the repolarization slope of MAP The T wave results from many simultaneous gradients between AP s during repolarization The peak of the T wave is expected to coincide with the maximum of these local gradients The maximum local gradient between two

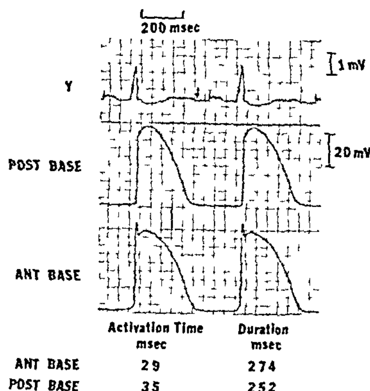


Fig 2 Typical experiment illustrating the differences between two MAP s from two different areas T wave is upright and bifid The arrow marks the end of the T wave Heart rate is kept constant by atrial pacing

plex averaged 50 7 ± 4 9 msec Table I shows the activation times (AT) in five areas on the ventricular surface expressed both as absolute durations and as per cent of the QRS duration The earliest AT was in the anterior middle and apical areas and the latest AT in the posterior basal area

Duration Table II shows the differences between MAP durations in simultaneously recorded MAP pairs from two different regions An example of such a pair is shown in Fig 2 Although the range of differences in Table II is wide most of the average differences between regions just attain significance (Table IV) In those experiments in which only one of the two simultaneously recorded MAP's was acceptable we expressed the duration of each MAP in per cent of the longest MAP duration in each dog (Table III) Table III shows that the longest MAP duration was at the apex and anterior base and the shortest MAP duration at the posterior base These results were similar to those in which pairs of MAP were recorded simultaneously However, Table IV shows that most of the average MAP duration differences between regions (Table III) are more significant than the average differences between the pairs of MAP s (Table II) probably due to the larger sample size in Table III than in Table II

Slope of repolarization The slope of terminal repolarization ranged from 0 3 to 0 54 volt per second In the same dog the repolarization slopes of different MAP s were nearly parallel (Fig 1) and did not deviate by more than 10 per cent from the average slope

Interval between the end of MAP and the end of the T wave Of 178 MAP s two ended 4 msec and 5 msec, respectively, after the end of the T wave and one ended simultaneously with the end of the T wave The remaining 175 MAPs ended before the end of the T wave (Fig 3) The average $MAP_e - T_e$ intervals in different areas ranged from 27 4 ± 11 7 msec at the posterior base to 21 3 ± 9 8 at the anterior base The difference between the pairs of MAP s (Table II), probably due to the larger sample size in Table III than in Table II

MAP duration and the onset of activation To analyze the relation between the AT and the duration of MAP independently of the area we arbitrarily subdivided all MAP s into three groups one with an early (8 to 20 msec) one with an intermediate (21 to 30 msec) and one with a late (> 31 msec) AT Table V shows that both the MAP s in Group I and in Group II are significantly longer than the MAP s in Group III

Discussion

Sequence of depolarization and repolarization The sequence of activation on the surface was from apex to base This result is in accord with the results of previous detailed studies of ventricular depolarization in the dog monkey and in man [10]

We found that the slopes of terminal repolarization in MAP s of different duration were approximately constant We have also shown that this slope was the same as the slope of TAP from the excised papillary muscles and trabeculae of the hearts of the same animals [11] These findings suggest that the intervals between the ends of MAP s represent the sequence of repolarization

Our study shows that this sequence on the ventricular surface is complex and geographically nonuniform This is in keeping with the results of previous studies with local bipolar electrograms [1] which indicated that inhomogeneities of repolarization occur within very small distances over the entire surface of the ventricles [12,13]

uggested that certain AP s terminate after the end of the T wave but do not generate de flections because they end simultaneously and undergo cancellation[9] We found no evidence in support of such ' silent repolarization on the ventricular surface This result is in agreement with our previous studies of MAP on the ventric ular surface of isolated rabbit hearts (A P Zumino L S Gettes and B Surawicz un published observation) and the endocardial sur face of human hearts[7]

Summary

Our study provides a reasonably detailed re polarization map of the ventricular surface in the dog heart The approximately constant repo larization slope of all MAP s on the surface sup ports the validity of the assumption that the *sequence of ventricular repolarization can be de* rived from the sequence of refractoriness Our results agree with the studies of functional refractory periods and show that the duration of recovery tends to shorten during the course of ac tivation This sequence is consistent with the positive ventricular gradient in the electrocar diogram

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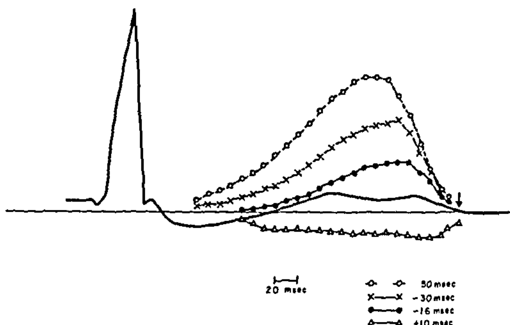


Fig 4 Magnified ventricular complex from Fig 2 (solid trace) with an additional four different T waves derived from the potential differences between two superimposed MAP's illustrated in Fig 4 measured in arbitrary units at 10 msec intervals during repolarization The solid circles mark the T wave derived from the MAP's superimposed in the same sequence as they occurred in the experiment (MAP at the anterior base ends 17 msec and MAP at the posterior base 33 msec before the end of the T wave) Other T waves represent potential differences between MAP's of the same configuration but after shortening or lengthening phase 2 of the MAP at the posterior base The T wave marked by crosses was constructed after the MAP at the posterior base was shortened by 14 msec this increased the MAP$_e$—T$_e$ difference between these two MAP's from 16 msec to 30 msec The T wave marked by empty circles is constructed after the MAP at the posterior base was shortened by 34 msec this increased the MAP—T$_e$ difference between these two MAP's to 50 msec The T wave marked by triangles was constructed after the MAP duration at the posterior base was increased by 26 msec this altered the MAP—T$_e$ sequence between these two MAP's and produced a negative T wave Note that the aT eT interval (second peak) of the recorded T wave is 40 msec and that the aT eT intervals of the derived T waves are 44 msec (dispersion 16 msec) 55 msec (dispersion 30 msec) and 75 msec (dispersion 50 msec)

AP's during repolarization may be expected during the inscription of the steepest repolarization slope of the AP which terminates earlier If we apply this to the entire heart the peak of the T wave should not occur before the onset of rapid repolarization in some portion of the ventricle This in turn suggests that the duration of the interval between the peak of the T wave (aT) and the end of the T wave (eT) bears a certain relation to the dispersion of repolarization in the entire heart In our study the interval between the peak (second peak if the T wave was bifid) and eT in Leads II or Y, averaged 33 ± 12 msec The precise relation between the dispersion of repolarization and the aT eT interval is not known but knowing the repolarization slope of the individual MAP we can calculate the probable upper limits of dispersion in an individual case An example of such a calculation is illustrated in Fig 4 This figure shows one ventricular complex from Fig 2 The MAP at the anterior base ends 17 msec and the MAP at the posterior base ends 33 msec before the end of the T wave Thus the dispersion of repolarization between these two MAP's was 16 msec The shape of the T waves was derived from the plot of 'potential differences' produced by superposition of these two MAP's when the dispersion of repolarization was unchanged (16 msec) and when the dispersion was shortened or prolonged by shortening or lengthening the MAP at the posterior base Fig 4 shows that unlike the recorded T wave the derived T waves have only one peak The timing of this peak is within the observed range of aT eT intervals when the dispersion of repolarization is 10, 16 or 30 msec but the peak occurs earlier than observed in any experiment when the dispersion is 50 msec This suggests that the dispersion of repolarization in dogs is less than 50 msec

Duration of MAP and QT interval In the study of Yanowitz, Preston and Abildskov's,[9] unilateral stellate ganglion stimulation was followed by an apparent lengthening of the QT interval This

sented in Table I and as may be seen there are no significant differences between the two groups concerning their clinical comparability Blood levels of lidocaine are presented in Fig 1 The 4 mg per minute group had significantly higher blood levels after only 15 minutes In the 2 mg per minute group lidocaine in the blood reached or exceeded 1 2 μg per milliliter at 120 minutes after the injection in three patients only and at 180 minutes in as few as seven patients In the 4 mg per minute group the mean blood level of lidocaine exceeded 1 2 μg per milliliter at 30 minutes and after 180 minutes all patients had blood levels exceeding 1 2 μg per milliliter The highest individual blood level during the first three hours after injection was 4 7 μg per milli liter which was observed in one of the 4 mg per minute patients at 180 minutes

Side effects Some of the patients in both groups experienced slight dizziness immediately following the bolus injection Apart from this no patient in either group experienced any discom fort that could be ascribed to lidocaine during the first three hours Concerning the 2 mg per minute group it was impossible to make any statements concerning side effects after that period since close observation ended at that time During the time of study (24 hours) the 4 mg per minute infusion was stopped in 10 cases for the following reasons in one case the cause was therapeutic failure and in two cases technical problems with the infusion pump In two cases lidocaine side effects were suspected (hypotension and impaired consciousness respectively) In these cases, the subsequent events however did not confirm these suspicions In five cases lido caine side effects were probable These patients were withdrawn at 260 minutes because of im paired consciousness (lidocaine in blood 2 1 μg per milliliter) at 780 minutes because of nausea (5 2 μg per milliliter) at 920 minutes because of blurred vision (3 2 μg per milliliter) at 280 minutes because of hypotension and at 650 minutes because of nausea The blood concentra tions of lidocaine were not available for the last two cases

Table I Selected data from the two groups of pa tients

	2 mg/min (n = 18) No	4 mg/min (n = 25) No
Sex		
Male	16	20
Female	2	5
Age		
30 39 years	1	1
40 49 years	2	1
50 59 years	6	14
60 69 years	7	8
70 79 years	2	1
Site of infarction		
Anterior	11	10
Posterior	4	11
Uncertain	3	4
Previous infarction		
0	12	20
1	3	3
≥2	3	2
Previous heart failure		
Yes	6	5
No	12	20
Left heart failure day of study		
Yes	6	2
No	12	23
Blood pressure (Mean ± S E M)		
Systolic	144 ± 4 7	138 ± 4 9
Diastolic	89 ± 3 4	88 ± 2 8
SGOT maximum (normal ≤20)		
≤20	1	0
21 100	11	11
101 200	3	11
>200	3	2
Creatinine mg/100 mL (normal ≤ 1 2)		
≤1 2	16	21
>1 2	2	3
Bilirubin, mg/100 mL (normal ≤ 1 2)		
≤1 2	18	21
>1 2	0	3

Discussion

In intravenous lidocaine treatment a plasma level of 1 2 μg per milliliter has been considered the lowest effective therapeutic level[10] A widely recommended dosage regimen is a bolus injection of about 1 mg per kilogram of body weight directly followed by a continuous infusion of 2 mg per minute With this intravenous dosage schedule it has been claimed that lidocaine blood levels above 1 2 μg per milliliter should be reached at about 20 minutes This statement is based upon results of normal volunteer subjects with the assumption that the distribution volume for lidocaine in patients with acute myocardial infarction is about half that of normal sub jects[2,11] The astonishingly low lidocaine blood levels reached in the present 2 mg per minute group with acute myocardial infarction do not confirm this.

One explanation might be lack of agreement

Blood levels of lidocaine after various infusion rates in patients with acute myocardial infarction

Lars Rydén
Anders Waldenstrom
Ylva Winsnes*
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Intravenous lidocaine is one of the most commonly used modes of treatment for ventricular tachyarrhythmias complicating acute myocardial infarction Although very potent lidocaine has been claimed ineffective in up to 20 per cent of patients [1,2] In intravenous lidocaine treatment, a bolus injection of about 1 mg per kilogram of body weight directly followed by a continuous infusion of 2 mg per minute has been recommended [2] Different studies have shown that lidocaine in this dosage regimen has an antiarrhythmic effect on ventricular tachyarrhythmias complicating acute myocardial infarction [3,4] However, Rydén and co workers[5] found that this amount of the drug resulted in astonishingly low blood levels during the first three hours following the start of therapy One explanation for therapeutic failure with lidocaine might be that commonly used amounts of the drug are too small to give a blood concentration within the therapeutic range To enable further conclusions concerning a reasonable dosage regimen, blood levels of lidocaine were determined following an infusion of 4 mg per minute in a group of patients with acute myocardial infarction These blood levels were then compared with those obtained when infusing 2 mg per minute

Materials and methods

The study was performed in patients admitted to a coronary care unit Only patients that subsequently fulfilled the World Health Organization (WHO) criterias[6] for acute myocardial infarction were included All patients had defined ventricular tachyarrhythmias which in accordance with the routine in the coronary care unit indicated lidocaine treatment [7]

Intravenous lidocaine (Astra Södertalje Sweden) was administered as a bolus injection of 75 mg during two minutes immediately followed by an infusion of 2 or 4 mg per minute respectively The infusion rate was kept constant by means of an infusion pump (Perfusor Braun Melsungen West Germany) A two per cent lidocaine solution was used The infusion was given into an arm vein through a short polyethylene cannula. The 2 mg per minute group has previously been described[5] and was studied for three hours The 4 mg per minute group was closely supervised as regards possible side effects for 24 hours Venous blood samples from the contralateral arm were taken at 15 30 60 120 and 180 minutes after the start of the injection The blood was frozen at −16° C and sent to the Astra Laboratories Sodertalje Sweden for lidocaine determinations. A gas chromatographic method was used.[8,9] Lidocaine levels were expressed as lidocaine base micrograms per milliliter of whole blood During the study serum concentrations of glutamic oxaloacetic transaminase bilirubin and creatinine were determined

Statistical comparisons were made using Chi square test and Student s t test.

Results

A total of 41 patients were included in the investigation of whom 16 belonged to the 2 mg per minute and 25 to the 4 mg per minute group Pertinent data concerning the patients are pre

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Posterior	4	11
Uncertain	3	4
Previous infarction		
0	12	20
1	3	3
≥2	3	2
Previous heart failure		
Yes	6	5
No	12	20
Left heart failure day of study		
Yes	6	2
No	12	23
Blood pressure (Mean ± S E M)		
Systolic	144 ± 4 7	138 ± 4 9
Diastolic	89 ± 3 4	88 ± 2 8
SGOT maximum (normal ≤20)		
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21 100	11	11
101 200	3	11
>200	3	2
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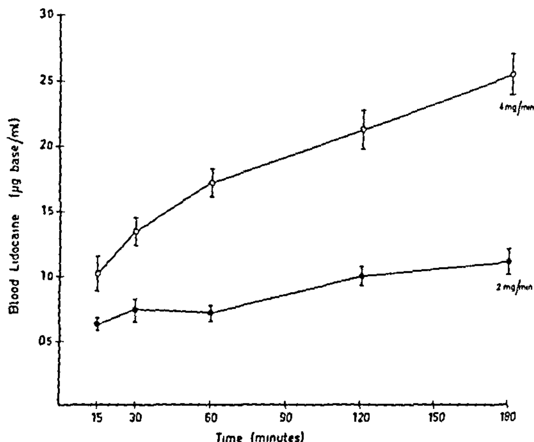


Fig 1 Blood levels of lidocaine base after intravenous administration of a 75 mg bolus injection followed by an infusion of 2 mg per minute and 4 mg per minute Mean level of the group ± S E M

concerning the method of expressing lidocaine levels and differences caused by determination of lidocaine in plasma or whole blood Such di vergences are however insufficient to explain the entire differences[5] Another and more proba ble explanation for the relatively low blood levels of lidocaine in the 2 mg per minute group is that the volume of distribution and the rate of meta bolic degradation of lidocaine in patients with acute myocardial infarction are more equal to that of normal persons than has been suggested The results in the 4 mg per minute group con firm this hypothesis as the blood levels are in agreement with previous results from normal subjects It is known that cardiac insufficiency as well as impaired hepatic function may be fol lowed by higher lidocaine blood levels[12 13] The pa tients in both groups were in a relatively good cir culatory condition despite their acute myocardial infarction and defined arrhythmias There is no reason to believe that the present patient materi al in this respect differs from what is usual in coronary care units

Although limited the data in the present study suggest that side effects of lidocaine are not nec essarily associated only with high blood levels Strong and Atkinson[14] reported an investigation in which patients with suspected side effects from lidocaine had normal or low plasma levels of the drug but high levels of metabolites That this might be an important factor for side effects has earlier also been suggested by Boyes and co workers[11] It must be remembered how difficult it is to differentiate between true side effects and symptoms derived from the acute myocardial in farction per se as these symptoms are very often of the same type as the side effects The symp toms of side effects during the 4 mg per minute infusion disappeared rapidly after stopping the infusion In the present closely supervised pa tient material lidocaine infusion was stopped im mediately after the onset of symptoms The con centration of lidocaine and/or metabolites at that time might be very near the toxic level for that patient and stopping the infusion then could cause a fairly rapid decrease below the toxic level This need not be contradictory to the known half life of lidocaine in blood at steady state kinetics[15]

Even considering a probably somewhat higher risk of side effects it seems justified to increase the routinely recommended infusion rate of lido caine to patients with acute myocardial infarc tion but without obvious signs of cardiac or

hepatic failure Our suggestion is to use 1 mg per kilogram of body weight as a bolus injection directly followed by 4 mg per minute for at least three hours An initially high infusion rate has also been suggested by Bassan and co workers [16] who in a recent study showed that there is a slow increase in levels of lidocaine following a con tinous infusion with a steady state level after only 10 hours In patients with obvious cardiac or hepatic failure the dose in the future as at pres ent must be balanced according to the clinical condition of the patient

Summary

Blood levels of lidocaine were estimated follow ing two different infusion rates in patients with acute myocardial infarction Forty one patients received lidocaine as a bolus injection of 75 mg directly followed by an infusion The infusion rate was in 16 patients 2 mg per minute and in 25 patients 4 mg per minute Blood levels of lido caine were determined at different times up to 180 minutes after the start of drug administra tion The levels in the 2 mg per minute group were lower than had been expected and the mean level ± S E was after three hours only 1 1 μg per milliliter Many of the 2 mg per minute patients did not during the time period observed, reach 1 2 μg per milliliter which has been con sidered as the lowest effective therapeutic level In the 4 mg per minute group mean level of lido caine already at 15 minutes was significantly higher than in the 2 mg per minute group (1 1 ± 0 14 and 0 6 ± 0 05 respectively $p < 0\ 05$) After three hours the mean blood level in the 4 mg per minute group was 2 6 μg per milliliter Although the blood levels were not followed after three hours a careful observation did not reveal any severe toxic effects in the 4 mg per minute group during next 21 hours In five cases however lido caine side effects were probable These symptoms disappeared rapidly after cessation of the infu sion In order to reach therapeutic blood levels of lidocaine within a reasonable time the infusion rate of 4 mg per minute is recommended at least for the first three hours

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Correlation between segmental early relaxation of the left ventricular wall and coronary occlusive disease

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Segmental abnormality of left ventricular wall contraction is a well known angiographic manifestation of ischemic heart disease During the past three years we have frequently noted segmental abnormality of left ventricular wall relaxation in patients undergoing angiography In a recent report Altieri and associates[1] described this type of abnormality which they termed segmental early relaxation phenomenon (SERP) They concluded that SERP was a normal variation of left ventricular relaxation In contrast we have found that when certain associated conditions are excluded there is a close correlation between SERP of the anteroapical left ventricular wall and occlusive disease of the left anterior descending coronary artery The purpose of this report is to describe this relationship and to emphasize the importance of a careful search for occlusive disease of the left anterior descending coronary artery in patients who demonstrate SERP of the anteroapical left ventricular wall on left ventriculography

Materials and methods

Between 10/18/71 and 4/30/73 305 patients underwent left ventricular angiography and coronary arteriography as a combined procedure in our cardiac laboratory (exclusive of postoperative restudies) These studies were performed by retrograde left heart catheterization using either the open arteriotomy technique from the right brachial artery or the percutaneous technique from the right femoral artery The contrast material used was 76 per cent meglumine diatrizoate sodium Left ventriculography was performed by injecting 40 c c of contrast material at 500 p s i with the patient in the right anterior oblique position A Cordis spring loaded power injector was used, with a total injection period of approximately two seconds During left ventriculography the electrocardiogram was recorded on high speed photographic paper using an Electronics for Medicine DR 8 recorder, with a marker indicating onset of injection Following left ventriculography selective coronary arteriograms were performed by multiple injections of six to eight c c of contrast media using a hand operated syringe In almost all instances the left coronary artery was filmed in three to five different projections and the right coronary artery was filmed in at least two projections Filming was performed at the rate of 60 frames per second using an Arriflex 35 mm camera mounted on a Phillips six inch image intensifier

Coronary arteriograms were evaluated for evidence of coronary occlusive disease and coronary artery lesions were graded by estimated percentage of luminal narrowing The left ventriculograms taken in the right anterior oblique projection were analyzed for left ventricular wall motion on rapid sequence projection and on frame by frame stop action projection For any contraction end diastole was defined by the cine frame immediately prior to the first frame show

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Fig 1 A through C Example of SERP involving large segment of anterior left ventricular wall in a patient with a 70 per cent stenosis in the proximal left anterior descending artery A Diagrammatic representation of sequential changes in left ventricular cavity shape traced from cineangiographic frames obtained in 30 degree RAO projection —— Left ventricular cavity shape at end diastole and end systole Left ventricular cavity shape at chronological mid systole Left ventricular cavity shape 64 msec after end systole B Cine frame at end systole C Cine frame 64 msec after end systole with SERP indicated by arrows



Fig 1B See legend for Fig *1 A* through *C*



Fig 1C See legend for Fig *1 A* through *C*

ing inward systolic movement of any portion of the left ventricular wall End systole was defined by the last cine frame showing inward movement of any portion of the left ventricular wall Mid systole was defined as the frame half way between the end diastolic frame and the end systolic frame

SERP was considered to be present when following end systole a segment of the left ventricular wall began definite outward motion before angiographic evidence of mitral valve opening and before outward motion was detected in the remainder of the left ventricular wall (Figs 1 and 2) Once this phenomenon has been observed and appreciated, it is usually readily apparent as a sudden outward segmental jerk followed by diastolic relaxation of the remainder of the ventricle Sometimes this phenomenon gradually developed during ventriculography being more marked on the later sinus beats of the ventriculogram than on the earlier sinus beats. To be considered as true SERP the abnormal early relaxation had to occur in the same area of the ventricular wall on at least two consecutive normally conducted sinus beats Ventricular ectopic beats and supraventricular beats with aberrant ventricular conduction (as determined by the simultaneously recorded electrocardiogram) were excluded from the analysis

Results

Of the 305 patients who had left ventriculograms and coronary arteriograms performed during the 18½ month period included in this study 50 were noted to have segmental early relaxation In every instance the abnormal relaxation occurred on the anterolateral or apical portions of the left ventricular wall. Of the 50 patients with SERP 14 had cardiac abnormality other than or in addition to coronary occlusive disease Six of these 14 patients had conduction abnormalities (right or left bundle branch block fascicular block or pre excitation) on the resting electrocardiogram six had valvular heart dis

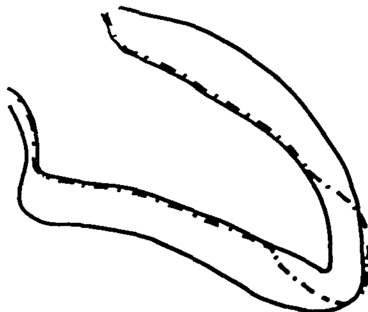


Fig 2 A through C Example of SERP involving apical segment of left ventricular wall in a patient with an 80 per cent stenosis in the mid portion of the left anterior descending coronary artery and a 90 per cent stenosis in the proximal diagonal branch A Diagrammatic representation of sequential changes in left ventricular cavity shape traced from cineangiographic frames obtained in 30 degree RAO projection —— Left ventricular cavity shape at end diastole and end systole Left ventricular cavity shape at chronological mid systole Left ventricular cavity shape 48 msec after end systole B Cine frame at end systole C Cine frame 48 msec after end systole with SERP indicated by arrows



Fig 2B See legend for Fig 2 *A* through *C*



Fig 2C See legend for Fig 2 *A* through *C*

ease one had non ischemic cardiomyopathy, and one had an atrial septal defect

When the 14 patients with any of the associated conditions noted above are excluded every one of the 36 remaining patients with SERP had significant coronary occlusive disease involving the left coronary arterial system Thirty five of the 36 patients had a stenosis 70 per cent or greater in the left anterior descending artery and in each case the lesion was proximal to the left ventricular wall segment demonstrating SERP The one patient with SERP and left coronary artery disease who did not have a left anterior descending artery lesion had total occlusion in the proximal left circumflex artery immediately distal to a small first obtuse marginal branch Of the 36 patients with SERP and left coronary artery disease, 34 had been studied angiographically because of chest pain Thirty one of these 34 patients had typical angina pectoris, and eight of these had anginal patterns which were considered unstable and preinfarctional Three patients had a chest pain which was atypical but still compatible with angina pectoris Two of the 36 patients with SERP and left coronary artery disease had no angina pectoris but were studied angiographically because they had experienced acute myocardial infarction at a young age

None of the 36 patients with SERP and left coronary artery disease had severe hypokinesis or akinesis of any portion of the anteroapical wall as viewed in the right anterior oblique projection Thirty three of the 36 patients had normal contraction of the anteroapical wall and three had mild to moderate hypokinesis of the same segment which demonstrated SERP The three patients with anterior hypokinesis all had classic electrocardiographic findings of previous anteroseptal myocardial infarction In the group

of 33 patients with normal contraction of the anteroapical wall the electrocardiographic findings were as follows two patients had low initial anterior QRS forces suggestive but not diagnostic of previous anteroseptal damage five had isolated precordial STT wave abnormality five had patterns of old inferior myocardial infarction with no abnormality in anterolateral leads 21 had no electrocardiographic abnormality

None of the 305 patients in our series had SERP of the inferior left ventricular wall as viewed in the right anterior oblique projection even when there was severe occlusive disease of the right coronary artery and/or left circumflex artery Since we do not have facilities in our laboratory to perform simultaneous biplane left ventriculography and since left ventriculograms were obtained in the left anterior oblique projection in only a few instances we were unable to evaluate the frequency of SERP involving the true posterior left ventricular wall or to correlate SERP of the posterior wall with coronary occlusive disease in the vessels supplying this area of the myocardium

Of the 305 cases included in this study 157 patients had stenosis of 70 per cent or greater in the left anterior descending artery Sixty three of these 157 patients had severe hypokinesis or akinesis involving the anterolateral and/or apical wall and none of these demonstrated SERP (Table I) Of the 94 patients who had 70 per cent or greater occlusion of the left anterior descending artery with normal contraction or mild to moderate hypokinesis of the anterolateral apical wall 35 (37 2 per cent) had SERP Of the 305 cases included in this study there were 49 who had neither significant coronary occlusive disease nor other recognized cardiac abnormality such as conduction abnormalities valvular heart disease congenital heart disease or non ischemic cardiomyopathy None of these 49 patients had SERP

Eight of the 35 patients with SERP and significant occlusive disease of the left anterior descending artery have had arteriographic restudy following aortocoronary bypass surgery (Table II) Three of these patients had no evidence of SERP on the postoperative left ventriculogram. In each of these three patients the graft to the left anterior descending artery was patent and there was no associated occlusive disease of any other vessel supplying the anterior lateral or

Table I Incidence of SERP

	Number of patients	*Number with SERP*	*Per cent with SERP*
LAD stenosis 70% or greater without severe anterior wall contraction abnormality	94	35	37 2
LAD stenosis 70% or greater with severe anterior wall contraction abnormality	63	0	0
No evident cardiac abnormality	49	0	0

Table II Analysis of patients with SERP restudied after saphenous vein grafting of left anterior descending artery (LAD)

	Number of patients
Patients undergoing restudy after saphenous vein grafting of LAD	8
Patients with no SERP on restudy	3
Patients with persistent SERP on restudy	5
LAD graft occluded	2
LAD graft open but associated nongrafted disease in vessels to anterior lateral, or apical wall	2
LAD graft open, with no associated disease in vessels to anterior lateral or apical wall	1

apical wall Two patients had persistent SERP on the postoperative left ventriculogram with an occluded graft to the left anterior descending artery Two patients had SERP on the postoperative left ventriculogram with a patent graft to the left anterior descending artery but with additional disease in vessels supplying the anterior or lateral left ventricular wall which was not bypassed (one had stenosis greater than 70 per cent in the first obtuse marginal branch and one had stenosis in both the first obtuse marginal branch and in a diagonal branch) Finally one patient had SERP on the postoperative left ventriculogram with a patent graft to the diseased left anterior descending artery and no other disease in the left coronary system

Discussion

Previous reports[2 5] have described segmental abnormalities of left ventricular contraction

More recently, attention has been directed to abnormalities of left ventricular relaxation Gooch and colleagues[6] described outward motion of the anterior left ventricular wall 'at the onset of diastole' in 16 of 23 patients with prolapsing mitral leaflet syndrome Ruttley and associates[7] noted a similar abnormality in normal patients and patients with coronary artery disease They localized the timing of this event to late systole prior to mitral valve opening, and noted that it occurred in areas of the left ventricular wall with good systolic contraction Altieri and co workers[1] recently described outward segmental left ventricular wall motion during the isovolumic relaxation period which they aptly termed segmental early relaxation phenomenon (SERP) They found SERP in 81 of 100 consecutive patients studied angiographically because of chest pain and confirmed the observation of Ruttley and associates[7] that SERP usually occurs in areas of the left ventricular wall which contract normally Although 59 of their 100 patients had coronary artery disease no attempt was made to correlate SERP with occlusive disease of the coronary arteries supplying the involved segment They concluded that SERP was a normal variation of left ventricular relaxation

Hamby and colleagues[8] reported 21 patients who demonstrated localized late systolic bulging of the left ventricular wall on angiography All of these patients were referred for evaluation of chest pain compatible with angina pectoris In every case the bulge was on the anterolateral or apical left ventricular wall Selective coronary arteriograms demonstrated significant coronary artery disease in 16 patients and normal coronary arteriograms in five patients Fifteen of 16 patients with coronary artery disease had disease of the left anterior descending artery Of the five patients with no significant coronary artery disease one had left anterior hemiblock and one had left bundle branch block on the resting electrocardiogram Five patients who were restudied after aortocoronary bypass surgery had normal contractile pattern with loss of the late systolic bulge

Several conclusions about SERP appear to be warranted based on the results of this study and the study by Hamby and co workers[8] Both studies suggest that segmental early relaxation may be a manifestation of myocardial ischemia SERP is usually found on the anterior or apical left ventricular wall and is usually associated with occlusive disease of the left anterior descending artery SERP does not appear to occur in areas with severe contraction abnormality and is most common in normally contracting segments Successful aortocoronary bypass surgery apparently eliminates SERP in some cases, presumably by relieving the underlying myocardial ischemia

Although the evidence suggests that SERP may be a manifestation of myocardial ischemia it has been reported in some patients with normal coronary arteries[1,7,8] It is possible that some of these patients in fact have regional myocardial ischemia in spite of angiographically normal macroscopic coronary arteries Most of these patients have been studied angiographically because of chest pain suggesting myocardial ischemia and they may have the syndrome of angina pectoris with normal coronary arteries as described by Kemp and colleagues[9] In any case it appears that myocardial ischemia may not be the only cause of SERP Eight of our 50 patients with SERP had valvular heart disease non ischemic cardiomyopathy or atrial septal defect Gooch and co workers[6] have reported a relationship between systolic prolapse of the mitral valve leaflets and SERP although the basis of this relationship is not clear An interesting recent report by LeWinter and associates[10] suggests that patients with mitral valve prolapse may have localized myocardial ischemia associated with increased left ventricular wall tension at the area of the base of the papillary muscles

There may also be a relationship between SERP and abnormalities of atrioventricular conduction and/or ventricular excitation Segmental early relaxation has been reported at the site of left ventricular pacing[11,12] Hamby and associates[8] have considered the possibility that the late systolic bulge in two of their cases with normal coronary arteries might be related to conduction abnormalities Six of our patients with SERP of the anteroapical wall had right or left bundle branch block fascicular block, or pre excitation on the resting electrocardiogram However, we have also seen patients with these conduction abnormalities who did not have SERP Further studies will be necessary to examine the possible relationship between SERP and conduction abnormalities

Summary

Fifty of 305 patients studied angiographically had segmental early relaxation phenomenon (SERP) of the anterolateral or apical left ventricular wall Fourteen of the 50 patients had cardiac abnormality other than or in addition to coronary occlusive disease Of the remaining 36 patients 35 had significant lesions in the left anterior descending artery (LAD) and one had occlusion of the proximal left circumflex artery SERP was noted in 35 (37 2 per cent) of 94 patients with LAD disease who did not have severe anteroapical contraction abnormality SERP was found in none of 49 patients who had neither significant coronary occlusive disease nor other cardiac abnormality Eight patients were restudied after bypass grafting of the LAD Three patients with patent grafts no longer demonstrated SERP Five had persistent SERP but four of these had occluded LAD grafts or nongrafted disease in other vessels supplying the anterolateral wall. Myocardial ischemia appears to be one cause but probably not the only cause of SERP

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Vascular reactivity to norepinephrine and hemodynamic parameters in borderline hypertension

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An altered responsiveness to the pressor effect of vasoactive agents has been commonly observed in hypertension Studies describing this effect have largely dealt with established hypertensive subjects with known etiology i e renovascular disease [1,2] primary aldosteronism [3,4] and pheochromocytoma [5] Similar results have also been reported on patients with essential hypertension [6-11] However borderline hypertension was never extensively examined

A number of factors have been postulated to explain the altered responsiveness to vasoactive agents[12-14] (1) availability of receptor to vasoactive agents (2) contractility of arteriolar smooth muscle fibers and (3) anatomic characteristics of arteriolar walls It seems improbable that the advanced vascular lesions of severe hypertension would play any major role in the reactivity of blood vessels to pressor agents in young patients with minimally elevated blood pressure, a short history of disease and no observable resultant functional impairment Hence it would seem reasonable that factors (2) and (3) play a minor role in the mechanism of the altered response to vasoactive agents and in consequence that factor (1) can be considered relatively dominant in this borderline group Clinical biological and hemodynamic evidence for significant neurogenic influences in primarily borderline hypertensive subjects has been described [15-20] and is in agreement with this assumption

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In order to help elucidate the above statement we have studied in borderline hypertensive subjects (1) the pressor responses to norepinephrine angiotensin, and isoproterenol and (2) the relationship between the pressor responses and the basal hemodynamic characteristics of the patients

Material and methods

Patients Eighty three untreated male hypertensive patients (mean age 34 ± 4 years) and twenty eight male normal subjects were included in the present study The patients were considered as borderline hypertensive subjects (41 cases) when, in the past twelve months at least one out of three casual pressure recordings showed a diastolic pressure of 90 mm Hg or more and one at least showed a diastolic pressure of less than 90 mm Hg The patients were considered to have a permanent hypertension (42 cases) when the diastolic pressure was constantly above 100 mm Hg during the past year The diagnoses were based on outpatient blood pressure recordings All the patients were untreated or had discontinued their therapy at least four weeks before the study They were hospitalized for six days and placed on a sodium diet of 100 milliequivalents per day They were submitted to extensive investigations including blood and urinary electrolytes catecholamine determinations endogenous creatinine clearance timed intravenous urography with wash out test and/or renal arteriography All the patients were listed as essential hypertensive subjects (Table I) None had cardiac or neurologic involvement Optic fundi were either normal (47 patients) or showed some venous nicking (36 permanent hypertensive subjects) Consent for in

Table I Clinical characteristics

	Normal subjects (1)	Borderline hypertensives (2)	Permanent hypertensives (3)	P values (1) (2)	(1) (3)	(2) (3)
No of patients	28	41	42			
Age (years)	34 ± 2	28 ± 1	41 ± 1	< 0 05	< 0 01	< 0 001
Weight (Kg)	66 ± 2	72 ± 1	75 ± 2	< 0 012	< 0 01	< NS
Height (cm)	169 ± 1	174 ± 1	172 ± 1	< 0 01	< NS	< NS
Body surface area (M^2)	1 76 ± 0 03	1 84 ± 0 03	1 87 ± 0 02	< 0 05	< 0 001	< NS

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vestigation was obtained after a detailed description of the procedure The protocol has been approved by INSERM (Institut National de la Sante et de la Recherche Medicale)

Hemodynamic parameters On the third day of hospitalization hemodynamic studies were performed after the patients had fasted overnight No premedication was administered Under local procaine anesthesia polyethylene catheters were introduced into the right brachial artery and median antecubital vein and were respectively advanced under fluoroscopic control into the aortic arch and the main pulmonary artery The arterial catheter was then put into the aortic root (Ar) immediately distal to the aortic valves for intra arterial pressure measurements and blood sampling for dye dilution curves With the subject in the supine position cardiac output was measured at least in duplicate using a Water s cuvette and densitometer as previously described [21] Indocyanine green (5 mg) was introduced into the pulmonary catheter and flushed at a precise time into the circulation in less than 0 5 second Using a constant rate pump blood was withdrawn from the arterial catheter and sent through the densitometer Blood was not reinfused. Before each study the system was recalibrated, using known dye concentrations and the same pump speed as during cardiac output determinations Cardiac index (CI) was expressed in milliliters per minute per square meter after correction for body surface area Mean arterial pressure (MAP) was measured with a Thomson Telco apparatus Total peripheral resistance (TPR) was calculated according to the following formula

$$TPR\ (dynes.\ sec\ cm^{-5}\ m^2) = \frac{MAP\ (mm\ Hg)}{CI\ (L/min./m^2)} \times 80$$

Blood volume determinations Cardiopulmonary blood volume (CPBV) was expressed as the volume between the main pulmonary artery and the tip of the arterial catheter It was calculated by the Stewart Hamilton method[22] as follows

$$CPBV\ (ml/Kg) = CI\ (ml/min/Kg) \times Tm\ (sec)(PA - Ar)$$

Tm (PA Ar) equals mean transit time *in seconds* from the pulmonary artery (PA) to the tip of the arterial catheter (Ar) The correction factor for the sampling system was substracted from the observed time in calculating the mean transit time

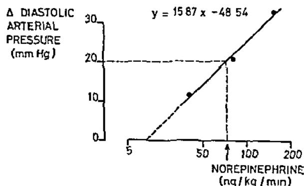


Fig 1 Log dose response curve of norepinephrine an example The arrow corresponds to the so called pressor dose of norepinephrine Legend Δ = increase

Prior to the hemodynamic study total blood volume (TBV) was measured in each patient in the recumbent position by the isotope dilution method using radioiodinated albumin as previously described.[21] After withdrawing a control sample 3 μCi were injected 10 minutes later a sample was taken to be counted The CPBV/TBV ratio was an estimation of the fraction of TBV in the heart and lungs

Vascular reactivity Vascular reactivity to norepinephrine[23] was studied in 46 patients Infusion of 5 per cent glucose was begun in an antecubital vein and the intra arterial blood

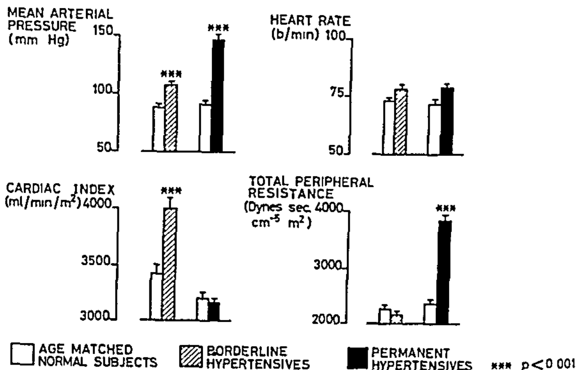


Fig 2 Basal hemodynamic parameters in comparison with age matched male normal subjects

pressure was checked Without disturbing the patient, the infusion was changed for one containing 16 mg of l norepinephrine base per 1 000 ml of glucose solution delivered at a given rate by a Harvard pump The infusate was prepared by the addition of 8 ml of the original l norepinephrine base solution (1 mg per 1 ml) to 500 ml of 5 per cent glucose in water The rate of infusion was successively increased every five minutes with the following doses 40 ng per kilogram per minute, 80 ng per kilogram per minute, and 160 ng per kilogram per minute Between each infusion the Harvard pump was stopped for 5 to 10 minutes in order to obtain the blood pressure baseline values The dose response curve was then plotted semi logarithmically (x axis = log dose per kilogram per minute y axis = increase in diastolic arterial pressure (mm Hg) (Fig 1) The so called pressor dose of l norepinephrine was calculated as the amount of l norepinephrine base per kilogram per minute necessary to obtain an increase in diastolic pressure of 20 mm Hg A similar method was used to determine the vascular reactivity to angiotensin[24] The pressor dose of angiotensin was the amount of angiotensin necessary to obtain an increase in diastolic blood pressure of 20 mm Hg The reactivity to isoproterenol hydrochloride was studied according to the method of George and co workers[25] The chronotrope dose was the amount of isoproterenol necessary to obtain an increase in heart rate of 25 beats per minute

Statistical study Statistical analysis using classical methods (difference of means correlations and stepwise regression) were performed[26] The correlation study examined relationships between the pressor dose of norepinephrine and the basal hemodynamic parameters Therefore all hemodynamic values were expressed per kilogram of body weight as was the pressor dose of norepinephrine

Results

Mean value study

Hemodynamic parameters (Table II) Borderline hypertensive subjects had a normal total peripheral resistance and increased cardiac index ($p < 0\,0001$) with a slight increase in stroke index and heart rate Permanent hypertensive subjects had a normal cardiac index and elevated total peripheral resistance ($p < 0\,0001$) Hemodynamic abnormalities were not related to age (Fig 2) Pulmonary right auricular and ventricular pressures were within normal ranges in both groups

Blood volume determinations (Table III) Total blood volume was significantly decreased ($p < 0\,0001$) in borderline and permanent hypertensive subjects Borderline hypertensive subjects had a cardiopulmonary blood volume significantly higher ($p < 0\,0001$) than permanent

Table II Basal hemodynamic parameters

	Normal subjects (1)	*Borderline hypertensives (2)*	*Permanent hypertensives (3)*	*P values*		
				(1) (2)	*(1) (3)*	*(2) (3)*
No of patients	28	41	4?			
SAP (mm Hg)	125 ± 2	141 ± 2	193 ± 6	<0 0001	<0 0001	<0 0001
DAP (mm Hg)	72 ± 2	89 ± 1	119 ± 3	<0 0001	<0 0001	<0 0001
MAP (mm Hg)	90 ± 2	108 ± 2	146 ± 4	<0 00001	<0 0001	<0 0001
CI (ml /min /M²)	3 359 ± 108	4 000 ± 112	3 152 ± 95	<0 0001	NS	<0 0001
CO (ml /min /Kg)	90 ± 4	104 ± 3	80 ± 8	<0 01	<0 05	<0 0001
SI (mL/M²)	46 ± 2	52 ± 2	42 ± 2	<0 05	<0 05	<0 0001
SV (mL/Kg)	1 25 ± 0 06	1 33 ± 0 04	1 05 ± 1 03	NS	<0 02	<0 001
HR (beats/min.)	73 ± 2	78 ± 2	77 ± 2	<0 05	<0 05	NS
TPR (dynes sec cm ⁵M²)	2 143 ± 96	2 162 ± 72	3 732 ± 171	NS	<0 0001	<0 0001

± 1 standard error of the mean

Legend SAP systolic arterial pressure DAP diastolic arterial pressure MAP mean arterial pressure CI cardiac index CO cardiac output SI stroke index SV stroke volume HR heart rate and TPR total peripheral resistance

Table III Basal blood volume determinations

	Normal subjects (1)	*Borderline hypertensives (2)*	*Permanent hypertensives (3)*	*P values*		
				(1) (2)	*(1) (3)*	*(2) (3)*
No of patients	12	41	42			
CPBV (mL/Kg)	14 79 ± 0 88	15 8 ± 0 51	12 91 ± 0 38	NS	NS	<0 0001
TBV (ml /Kg)	78 67 ± 1 71	72 02 ± 1 40	70 68 ± 0 96	<0 005	<0 0001	NS
CPBV/TBV (%)	18 57 ± 1 01	21 71 ± 0 60	17 9 ± 0 5	<0 01	NS	<0 001
Hematocrit (%)	44 ± 1	44 ± 1	44 ± 1	NS	NS	NS

Legend. CPBV cardiopulmonary blood volume and TBV total blood volume
± 1 standard error of the mean
n 28 in this control group

hypertensive subjects The CPBV/TBV ratio was significantly higher in borderline hypertensive subjects in comparison with normal (p < 0 01) and permanent hypertensive subjects (p < 0 001)

Vascular reactivity (Table IV) The pressor dose of norepinephrine was significantly higher in borderline and permanent hypertensive subjects (p < 0 001) but the standard error of the mean was much more important in permanent hypertensive subjects The chronotrope dose of isoproterenol was lower in permanent hypertensive subjects (p < 0 01) No difference was observed for the pressor dose of angiotensin

Correlation study The correlation coefficients between the pressor dose of norepinephrine and the hemodynamic parameters were determinated in each group

Borderline hypertensive subjects (Table V) The pressor dose of norepinephrine was positively correlated to the cardiac output (p < 0 001) (Fig 3) the stroke volume (p < 0 001) the cardiopulmonary blood volume (p < 0 0001) (Fig 4) the total blood volume (p < 0 02) and the CPBV/TBV ratio (p < 0 01) Such correlations were not observed with isoproterenol and angiotensin

Permanent hypertensive subjects (Table V) A significant negative correlation (p < 0 0001) was observed between the pressor dose of norepinephrine and the diastolic (Fig 5) or mean arterial pressure

Comments

It has been well established that the principal hemodynamic characteristic of borderline hypertension is a high cardiac output (see review in[16]) The two most significant observations of the present study concern the pressor dose of norepinephrine in borderline hypertensive subjects (1) the pressor dose is increased, a fact which suggests the role of availability of receptor sites to the vasoactive agent and (2) there is a strong positive correlation between the pressor dose of norepinephrine and the basal cardiopulmonary blood volume (and also the cardiac output) Such

Table IV Vascular reactivities

	Normal subjects (1)	Borderline hypertensives (2)	Permanent hypertensives (3)	P values		
				(1) (2)	(1) (3)	(2) (3)
No of patients	12	24	22			
Pressor dose of norepinephrine (ng /Kg /min)	133 ± 22 1	263 2 ± 31	409 8 ± 117 3	<0 0001	<0 001	NS
Pressor dose of angiotensin (ng /Kg /min)	8 03 ± 0 99	9 23 ± 1 2	8 56 ± 1 3	NS	NS	NS
Chronotrope dose of isoproterenol (γ)	2 63 ± 0 45	2 10 ± 0 30	4 2 ± 0 80	NS	<0 01	<0 01

± 1 standard error of the mean

Table V Correlation coefficients (r values) between the pressor dose of norepinephrine and the basal values of hemodynamic parameters

Correlation of the pressor dose of norepinephrine with	Borderline hypertensives (n = 24)		Permanent hypertensives (n = 22)	
	r value	P value	r value	P value
SAP (mm Hg)	+ 0 27	NS	- 0 49	<0 02
DAP (mm Hg)	+ 0 29	NS	- 0 67	<0 005
MAP (mm Hg)	+ 0 30	NS	- 0 65	<0 005
HR (beats/min)	+ 0 06	NS	- 0 05	NS
CO (ml /min /kg)	+ 0 58	<0 005	+ 0 09	NS
SV (ml /kg)	+ 0.53	<0 01	+ 0 04	NS
TPR (Dynes sec cm $^{-5}$ kg)	- 0 52	<0 01	- 0 39	NS
CPBV (ml /Kg)	+ 0 70	<0 001	+ 0 12	NS
TBV (ml /Kg)	+ 0 49	<0 02	+ 0 25	NS
CPBV/TBV (%)	+ 0 60	<0 01	- 0 08	NS

Legend for abbreviations see Tables II and III

results suggest an important role for the adrenergic nervous system in the mechanism causing an elevation of blood pressure in borderline hypertensive patients

An increase in cardiac output can be caused by central or peripheral factors [27] Cardiac factors include an increase in stroke volume and an increase in heart rate Our study demonstrates that increased stroke volume is the dominant, though not unique factor causing the raised cardiac output However, neither an increased stroke volume nor an increased heart rate by themselves will cause a sustained increase in cardiac output if all peripheral factors are maintained constant [27] The increase in stroke volume observed implies therefore, that an increased venous return is involved in the mechanism of elevation of cardiac output in our borderline hypertensive patients

The blood volume in borderline hypertension is normal or low [17] Thus, an increased venous return and hence, cardiac output in these patients cannot be explained by invoking an expansion of blood volume However an increase in mean circulatory pressure and hence venous return can be achieved in conditions of normal or low blood volume by a decrease in the compliance of the capacitance vessels in the peripheral circulatory system One way of demonstrating such a decreased compliance is to show a concomitant increase in the estimated value of cardiopulmonary blood volume As previously described,[2] cardiopulmonary blood volume mean value was higher in borderline hypertensive subjects but the difference was not significant in comparison with normal subjects The main result of the present study was to demonstrate an increased CPBV/TBV ratio in comparison with both normal and permanent hypertensive subjects Therefore this data shows that there is a definite redistribution of intravascular blood volume in borderline hypertensive subjects

It has been well established that the constriction of capacitance vessels is related to neurogenic influences or to the presence of vasoactive agents Borderline hypertensive patients have

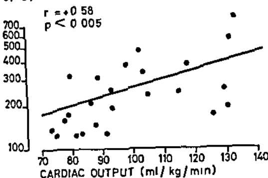


Fig 3 Correlation between the pressor dose of norepinephrine and the basal cardiac output in borderline hypertensive subjects (semi logarithmic scale)

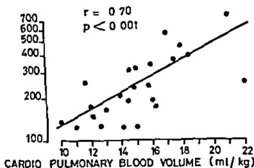


Fig 4 Correlation between the pressor dose of norepinephrine and the basal cardiopulmonary blood volume in borderline hypertensive subjects (semi logarithmic scale)

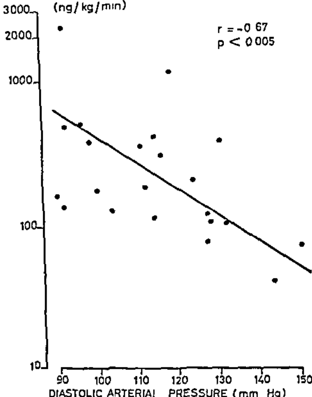


Fig 5 Correlation between the pressor dose of norepinephrine and the basal diastolic blood pressure in permanent hypertensive subjects (semi logarithmic scale)

increased values of both CPBV/TBV ratio and pressor dose of norepinephrine In addition the pressor dose is directly correlated to the cardiopulmonary blood volume and the cardiac output These results highly suggest that the pressor response to norepinephrine and the sympathetic activity are causally related in borderline hypertension A lack of such correlation is demonstrated for angiotensin and isoproterenol pointing to a specific norepinephrine like mechanism for this effect Thus we tentatively conclude that enhanced venous tone and increased venous return are involved in the mechanism of production of high cardiac output in borderline hypertensive patients

No comparable result is observed in the permanent hypertensive group A wide range in pressor dose of norepinephrine was observed The main result was a significant negative correlation between the pressor dose of norepinephrine and the diastolic or mean blood pressure So only patients having a high blood pressure elevation have really an increased responsiveness to norepinephrine [6,9] Such observations (in the permanent group) could be explained by the advanced stage of the disease Anatomic changes and/or altered functional characteristics of arterial walls have been shown to result in alterations in the normal reactivity to pressor agents by the vessel walls [13,14] Arterial lumen diameters fall due to the structural changes and they cause logarithmically proportional rises in peripheral arterial resistance and therefore blood pressure [12]

Significant differences do exist in the regulation of blood volume and its distribution in borderline and permanent hypertensive subjects It has been suggested that borderline hypertension may be an early stage in the natural history of hypertensive disease [7,9] The initiating chain of events in the development of hypertensive dis

Table IV Vascular reactivities

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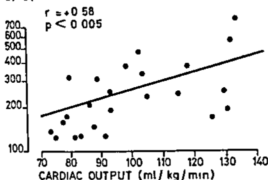


Fig 3 Correlation between the pressor dose of norepinephrine and the basal cardiac output in borderline hypertensive subjects (semi logarithmic scale)

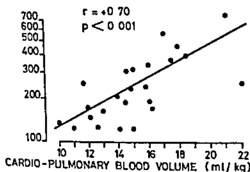


Fig 4 Correlation between the pressor dose of norepinephrine and the basal cardiopulmonary blood volume in borderline hypertensive subjects (semi logarithmic scale)

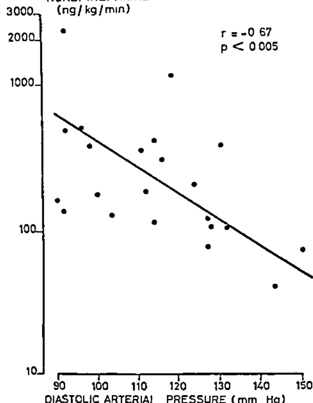


Fig 5 Correlation between the pressor dose of norepinephrine and the basal diastolic blood pressure in permanent hypertensive subjects (semi logarithmic scale)

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Significant differences do exist in the regulation of blood volume and its distribution in borderline and permanent hypertensive subjects It has been suggested that borderline hypertension may be an early stage in the natural history of hypertensive disease [7 9] The initiating chain of events in the development of hypertensive dis

ease may well be enhanced sympathetic tone which affecting the compliance vessels predominantly causes an increased venous return, thus raising cardiac output and blood pressure

Summary

Pressor response to norepinephrine, cardiopulmonary blood volume, and hemodynamic parameters were studied in 41 borderline hypertensive patients in comparison with 42 permanent essential hypertensive patients and 28 normal subjects Borderline hypertensive subjects had a high cardiac index ($p < 0.0001$) normal total peripheral resistance and low total blood volume ($p < 0.005$) The ratio between cardiopulmonary blood volume (CPBV) and total blood volume (TBV) was significantly higher in comparison with normal subjects ($p < 0.01$) and permanent hypertensive subjects ($p < 0.001$) The pressor dose of norepinephrine was elevated ($p < 0.0001$) and was directly correlated with the basal values of the cardiac output ($p < 0.005$) the cardiopulmonary blood volume ($p < 0.001$) and the CPBV/TBV ratio ($p < 0.01$) None of these results was observed in permanent hypertensive subjects the only significant result was a negative correlation between the pressor dose of norepinephrine and the basal diastolic arterial pressure ($p < 0.0001$) This study provides evidence that the cardiac output elevation in borderline hypertensive subjects was related to increased venous return and enhanced sympathetic venous tone

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Mechanism of immediate hemodynamic effects of chlorothiazide

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The thiazide diuretics have been used extensively for the treatment of hypertension ever since the late 1950 s but their precise mode of antihyper tensive action still remains to be understood A decreased cardiac output may play some role for the early hypotensive effect[1,5] but the mecha nism for this reduction is still unknown and the long term hemodynamic effects remain unre solved. Other possible means for their hypoten sive action have been suggested including de creased plasma and extracellular[1,2,6,9] and in tracellular fluid volumes[10,11] net total body[7] and artery wall[12] sodium depletion altered vascular responsiveness[1,5,12,13] and altered neural ac tivity[14] Although it was held initially that the plasma and extracellular fluid volumes returned to pretreatment levels[3,14] more recent evidence has shown that volume contraction persists for as long as two years in hypertensive patients treated only with thiazide congeners[7,9]

Since cardiac output is reduced acutely[4,5,13,15,16] the present study was designed to evaluate its possible association with fluid volume contrac tion This relationship if established, could pro vide further insight into a better understanding of the long term antihypertensive effects Moreover it is of great importance to know whether the immediate output reduction is in fluenced by impaired myocardial contractility a decreased right atrial return resulting from venous pooling (as suggested by earlier studies) or whether it is only achieved by a prompt volume loss initiated by diuresis

Methods

Acute hemodynamic effects of chlorothiazide (25 mg per kilogram intravenously) were studied in 22 mongrel dogs of both sexes weighing from 10 to 25 kilograms These dogs were anesthetized with sodium pentobarbital (35 mg per kilogram) and artificially ventilated by a Harvard respira tor A femoral artery and vein were cannulated with a PE 240 tubing for pressure measurements (P23Db Statham transducers) and drug adminis tration After entering the chest through an inci sion in the fourth or fifth intercostal space the pericardium was opened and an electromagnetic flow probe (Micron Instruments, inner diameter 12 14 or 16 mm) was placed around the ascend ing aorta The left ventricle was cannulated transmurally with teflon tubing (Angiocath No 14) for recording intraventricular pressure Thus aortic ventricular and central venous pressures as well as phasic and mean aortic blood flow were continuously recorded on a Hewlett Packard multichannel recorder Here after mean aortic blood flow will be referred to as cardiac output acknowledging that coronary flow was excluded. The first derivatives of left ventricular pressure and aortic flow were ob tained from recordings at 100 mm per second paper speed over one full respiratory cycle The left ventricular end diastolic pressure was deter

From th Un rsity f Oklahom Health Sc en es Center Oklahoma City Okl

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mined from similar high speed recordings using a 0 to 40 mm Hg pressure scale

Chlorothiazide 25 mg per kilogram, was administered intravenously over a one minute period in a distilled water solution (25 mg per milliliter concentration) after four control measurements, at five minute intervals, were recorded Four separate experiments were conducted in these 22 dogs

Hemodynamic effects Hemodynamic measurements were obtained during two successive 20 minute periods (pre and postchlorothiazide) in 14 dogs Serum sodium potassium, chloride, and total protein concentrations in addition to arterial hematocrit were measured before and twenty minutes after the diuretic The electrolytes were measured by flame photometry with an internal standard and plasma protein by the standard Biuret method

Volume replacement studies In six of these 14 dogs which were studied hemodynamically both ureters were cannulated and the urine volume was measured at five minute intervals Urine osmolality and sodium potassium and chloride concentrations were determined for the pre and posttreatment periods These studies were performed in order to determine whether the urinary volume loss measured during the immediate 26 minutes following chlorothiazide administration was sufficient quantitatively to account for the observed hemodynamic changes This was accomplished by intravenously infusing 6 per cent Dextran in 0 9 per cent sodium chloride over a six minute period Then after a subsequent stabilizing period, a second Dextran infusion was performed using a volume calculated to exceed the urine volume (at the time of the end of the infusion) by approximately 25 ml

Ureterocaval anastomosis In eight additional dogs both ureters were cannulated as above but the entire urine flow was shunted back into the inferior vena cava in order to prevent volume loss by diuresis These experiments were performed to determine whether the immediate hemodynamic responses to chlorothiazide were solely attributable to the diuretic effect of the drug Hemodynamic measurements were obtained as described above Then 20 minutes after chlorothiazide administration a controlled hemorrhage was instituted (a measured withdrawal of blood over a five minute period) in order to simulate quantitatively the thiazide induced volume loss measured in the studies described above The consequent hemodynamic effects were recorded over the ensuing five minutes (see above)

Hemorrhage In order to determine whether the hemodynamic effects of intravascular volume contraction were influenced by chlorothiazide per se four of the eight dogs described above were hemorrhaged before and after thiazide Thus, prior to chlorothiazide administration blood was withdrawn and after a five minute observation period the blood was reinfused and the control period was started after another five minute observation period Then, as described above the same volume of blood was withdrawn 20 minutes after thiazide administration

Results

Hemodynamic effects During the 20 minutes after chlorothiazide was administered there was a progressive and significant fall in cardiac output (18 per cent) peak aortic flow (11 per cent) maximum aortic flow acceleration (7 per cent) left ventricular ejection time (6 per cent) mean systolic ejection rate (13 per cent) left ventricular end diastolic pressure and central venous pressure (Table I File B) The reduction in cardiac output was due to a fall in stroke volume because heart rate remained stable throughout Mean arterial pressure did not change significantly, indicating an increased total peripheral resistance through a fall in cardiac output Left ventricular dp/dt remained unchanged.

Hematocrit and serum protein concentration increased The serum potassium and sodium concentrations fell while chloride concentration remained stable Plasma renin activity (bioassay) increased significantly in the six dogs studied (Table II)

Volume replacement studies In the six studied dogs urine flow increased from 0 33 ml per minute during the control period to 2 4 ml per minute (+727 per cent) after chlorothiazide administration (Table II) This diuretic effect started immediately during the one minute injection period and remained stable throughout the ensuing 25 minutes this diuresis accounted for a 61 ml (average) loss of fluid volume Urinary osmolality and potassium concentration decreased in all six dogs after chlorothiazide

Table I Hemodynamic effects of chlorothiazide

			Cardiac output (ml./min.)	*Peak aortic flow (ml./sec.)*	*Flow acceleration (ml./sec²)*	*LV dp/dt (mm. Hg/sec.)*	*Mean arterial pressure (mm. Hg)*	*LV end diastolic pressure (mm. Hg)*	*Central venous pressure (mm. Hg)*	*Heart rate (beats/min.)*
A	Controls	b	1 811	136	4 623	2 208	97	7 6	3 3	145
	15	a	1 793	134	4 535	2 202	99	7 4	3 3	147
	minutes	d	−18	−2	−97	−6	+2	−0 2	±0	+2
	n=22	p<	ns	ns	ns	ns	ns	ns	ns	ns
B	Chlorothiazide	b	1 797	133	4 432	2 131	102	7 7	2 9	150
	diuresis not	a	1 483	119	4 138	2 192	104	6 7	2 1	151
	prevented	d	−314	−14	−294	+61	+2	−1 0	−0 8	+1
	n=14	p<	0 001	0 001	0 005	ns	ns	0 005	0 05	ns
C	Volume correction	b	1 485	113	3 832	2 020	105	6 7	2 1	158
	after	a	1 785	125	4 217	2 180	110	7 8	2 5	151
	chlorothiazide	d	+300	+12	+385	+160	+5	+1 1	+0 4	−7
	n=6	p<	0 005	0 001	0 05	ns	0 01	0 05	ns	0 05
D	Chlorothiazide	b	1 787	138	4 716	2 327	93	7 0	4 2	143
	diuresis pre	a	1 755	137	4 848	2 327	98	7 2	4 4	139
	vented	d	−32	−1	+132	0	+5	+0 2	+0 2	−4
	n=8	p<	ns	ns	ns	ns	ns	ns	ns	ns
E	Hemorrhage	b	1 755	137	4 848	2 327	98	7 2	4 4	139
	after	a	1 526	124	4 420	2 180	92	6 5	3 9	143
	chlorothiazide	d	−229	−13	−428	−147	−6	−0 7	−0 5	+4
	n=8	p<	0 005	0 001	0 02	0 01	0 01	0 05	0 05	ns
F	Hemorrhage	b	2 095	157	5 330	2 255	92	6 1	5 1	145
	before	a	1 784	140	4 900	2 090	88	5 7	4 5	148
	chlorothiazide	d	−311	−17	−430	−165	−4	−0 4	−0 6	+3
	n=4									

b bef e afte and d, diff rence due to hloroth az d (hles B a d D) volume rr ti n (C) h morrhage (E and F) and controls (A) n numb r of studie = me di ect n l h ng in all f ur dogs of gr up F n not gn ficant

urine sodium and chloride concentrations remained essentially unchanged (Table II) Volume replacement was then achieved by infusing 6 per cent Dextran in saline (61 ml average) and all reduced hemodynamic indices returned to prechlorothiazide control levels (Table I File C) With further volume infusion calculated to exceed the total urinary volume excretion by an additional 25 ml these hemodynamic functions continued to rise above the prechlorothiazide levels

Ureterocaval anastomosis In the eight additional dogs that underwent ureterocaval anastomosis in order to prevent diuresis induced volume depletion there were no significant hemodynamic alterations observed during the 20 minutes following chlorothiazide (Table I File D) And as might be expected hematocrit remained stable However after the 61 ml. controlled hemorrhage (calculated to be equivalent to the volume lost by diuresis if that could have occurred) the same hemodynamic changes were observed as in those dogs with thiazide induced diuresis (but without ureterocaval anastomosis) (Table I compare Files B and E)

Hemorrhage To determine whether chlorothiazide per se altered the hemodynamic changes produced by volume contraction four of the eight dogs with ureterocaval anastomoses were hemorrhaged before and after receiving the diuretic No hemodynamic differences were observed thus following the slow withdrawal of 61 ml of blood, the cardiac output reduction and other hemodynamic changes were not significantly different before and after chlorothiazide (Table I Files E and F)

Discussion

The results of these studies demonstrate that chlorothiazide produced an immediate fall in cardiac output and stroke volume paralleled by decreased left ventricular end diastolic and central venous pressures These hemodynamic effects were directly associated with and depen

Table II Diuretic effects of chlorothiazide

		Before	After	d(abs)	d (%)	p<
A Urinary excretions (n=6)						
Volume	ml/min	0 33	2 42	+2 09	+633	0 005
K^+	mEq/min	0 058	0 155	+0 098	+168	0 005
Na^+	mEq/min	0 043	0 375	+0 332	+772	0 001
Cl^-	mEq/min	0 035	0 264	+0 229	+654	0 001
Osmolality	mOsm/min	0 385	1 316	+0 931	+242	0 005
B Urinary concentrations (n=6)						
K^+	mEq/L	175	64	-111	-63	0 001
Na^+	mEq/L	130	155	+ 25	+ 19	ns
Cl^-	mEq/L	105	109	+ 4	+ 4	ns
Osmolality	mOsm/L	1 168	544	-624	- 53	0 01
C Blood chemistry (n=14)						
Hematocrit	%	33 5	35 1	+ 1 6	+ 5	0 001
Serum protein	Gm %	6 43	6 57	+ 0 14	+ 2	0 005
K^+	mEq/L	3 25	2 95	- 0 3	- 9	0 01
Na^+	mEq/L	145 2	143 7	- 1 5	- 1	0 05
Cl^-	mEq/L	110 8	110 8	±0	0	ns
Plasma renin activity (n=5)	mg/10 ml	39	54	+ 15	+ 38	0 05

d difference (absolute and in per cent of controls) n number of animals ns not significant

dent upon a volume loss brought about through diuresis That this was a cause effect relationship is shown by the return of all hemodynamic indices to pretreatment levels after volume correction with Dextran infusion and because these hemodynamic changes were completely *prevented* by ureterocaval anastomosis This association was all the more striking in realizing that a small contraction of fluid volume (61 ml) brought about in 20 minutes time was associated with a rather large (18 per cent) reduction in cardiac output

The finding of an immediate decrease in cardiac output and stroke volume confirms our earlier report [5] and is in agreement with results in normotensive and hypertensive men in whom these observations were made within one to three hours after intravenous chlorothiazide [4,13,15,16] That the decreased cardiac output could not be caused by a negative inotropic action of the thiazide compound itself was shown by the stability of left ventricular dp/dt and aortic flow acceleration following the drug and when diuresis was prevented by ureterocaval anastomosis (Table I, File D) And this same line of reasoning seems to exclude a venodilator action of the thiazide Electrolytic changes also seemed to be unimportant with respect to this effect since with only volume correction the hemodynamic changes returned to prechlorothiazide control levels (despite a further decrease in serum potassium concentration) This finding is of some importance since recent studies have shown an increased cardiac output in patients with primary hyperaldosteronism[17] one possible explanation, hypokalemia does not seem to be confirmed by these studies

Hence the most likely cause of the decreased cardiac output is a diminished venous return brought about by volume contraction This is indicated by the reduced central venous and left ventricular end diastolic pressures Earlier studies in men[13,15,16] also demonstrate a decreased filling pressure of the right and left heart however this phenomenon was believed to result from a redistribution of blood into the peripheral circulation, possibly through thiazide induced venodilation[4,5,13,15,16] Since the present studies demonstrated that the decreased filling pressure was dependent upon volume loss the heretofore unproved assumption of a thiazide induced venodilation no longer seems tenable

That the diuretic effect resulted in a decreased plasma volume is indicated by the rise in hematocrit and serum protein concentration (Table II) These data permitted calculation of 7 and 4 per cent decreases, respectively in plasma volume Assuming a plasma volume of 44 ml per kilograms in a 17 kilogram dog [18] the observed urine volume after 20 minutes (48 ml) represents 6 per

cent of the anticipated plasma volume confirming that the main source of the excreted urinary volume came from the circulating plasma volume The total potassium excreted during this 20 minute postthiazide period was 3 mEq but the serum potassium concentration fell by only 0 3 mEq per liter Thus much of the excreted potassium must have originated from extra plasma sites

For the immediate postthiazide phase no significant changes in hematocrit have been reported.[13,15] However in one study there was a slight tendency toward an increased hematocrit[15] and decreased plasma volume [13] In other reports the hemoconcentration most likely was masked by a volume infusion.[6,13,16]

Methodologically electromagnetic measurement of flow is to some degree dependent upon hematocrit An increased hematocrit could result in an erroneously low measurement of blood flow However according to our own calibrations (with bloods of different hematocrit) an increase of hematocrit from 33 5 to 35 1 (as observed in our study) would result in a one per cent reduction in measured flow a value too low to account for the 18 per cent reduction in cardiac output observed after chlorothiazide

No hypotensive effect of chlorothiazide was found during these acute studies However these data should not be construed to indicate that the observed hemodynamic and diuretic effects are unrelated to the clinically observed antihypertensive effect since the thiazides lower blood pressure mainly in the presence of hypertension [12,16,19] Nevertheless these studies point up the close interrelationship of hemodynamic and fluid volume alterations during thiazide therapy and the need to refocus attention upon these factors in long term experimental and clinical studies if the antihypertensive mechanism is ever to be completely understood. Thus if volume contraction and cardiac output reduction are prompt and unassociated with pressure reduction further studies are indeed necessary to explain the subsequent fall in pressure

Finally it is also interesting to compare these hemodynamic findings with chlorothiazide in anesthetized dogs with those obtained with propranolol in similarly anesthetized dogs[20] and hypertensive man [21,22] Thus with these two very dissimilar compounds (one a diuretic and the other a beta adrenergic receptor blocking agent) both decrease output immediately only to reduce arterial pressure with time[21,22] and both have been shown to be the only antihypertensive compounds to be associated with a contracted plasma volume on prolonged therapy [23] Perhaps then the mechanism for the reduction of pressure with these two compounds may shed new information concerning the maintenance of the elevated arterial pressure in hypertensive man

Summary

The mechanism of the immediate hemodynamic effects of intravenous chlorothiazide (25 mg per kilogram) was studied in 22 anesthetized open chest dogs Within 20 minutes after administration cardiac output and stroke volume significantly fell this was associated with decreased central venous and left ventricular end diastolic pressures That these hemodynamic effects were caused by and dependent upon volume loss through diuresis (eightfold increase in urine volume) was shown by a return of these measurements to control levels when the volume loss (by diuresis) was corrected with 6 per cent Dextran by prevention of the hemodynamic changes in chlorothiazide treated dogs previously prepared with ureterocaval anastomosis and by confirming these same hemodynamic effects by quantitatively equivalent hemorrhage Thus the immediate diuresis produced by chlorothiazide resulted in a contracted plasma volume (increased hematocrit and serum protein concentration) which in turn diminished cardiac venous return central filling pressures stroke volume and cardiac output There was no evidence demonstrated to indicate any direct myocardial effect or peripheral venodilation induced by the thiazide

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Cardiac effect of diuretic drugs

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It is well established that diuretic drugs affect the re absorption of sodium and potassium in the renal tubule [1,2] Only a few studies have shown an extra renal site of diuretic drug action There is evidence that ethacrynic acid[3] and the potassium sparing agent triamterene [4] act on red cell membrane adenosinetriphosphatase (ATPase) as well as renal tubular cells Except for work done in our laboratories no conclusive evidence for a cardiac site of action of these drugs has been presented.[5] The potassium sparing diuretics triamterene and amiloride suppress the renal tubular secretion of potassium while ethacrynic acid and furosemide are potent kaliuretic agents [6,8] The purpose of this paper is to report studies demonstrating a myocardial effect of these drugs The potassium sparing agents triamterene and amiloride reduced the digitalis induced increase in cardiac A V difference of potassium while ethacrynic acid and furosemide magnified the digitalis induced A V difference of potassium

Since myocardial potassium loss is believed to underlie the development of digitalis induced arrhythmias the potassium sparing drugs may prevent digitalis induced arrhythmias by myocardial action as well as by preventing potassium depletion Ethacrynic acid and furosemide may potentiate digitalis induced arrhythmias by enhancing myocardial potassium loss in addition to renal potassium wasting

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Th s project wa s pported, n p rt, by f ds from the N tional Institutes of H lth Gra t No R01 HE12463

Repri t equest D Robe t H S ll r P of so nd Ch m n Departm t f F m ly Med i Medi l School of the State Un e sity f New Yo k t B f l c/o Deaconess Hosp tal, 1001 Humboldt Pkwy B f lo N Y 14208

Methods and materials

In all studies mongrel dogs with an average weight of 20 kilograms were anesthetized with intravenous pentobarbital and ventilated through a cuffed endotracheal tube with 100 per cent oxygen using a Harvard ventilator adjusted to the dog s weight There was no significant difference in the mean weights of the different groups Under fluoroscopic guidance one catheter was placed in the coronary sinus and another catheter in the right atrium The location of the catheters were checked visually and also by simultaneous determinations of Po_2 in mixed venous blood from the right atrium and in the coronary sinus blood. Simultaneous samples from the femoral artery and coronary sinus were obtained twice during a control period and at 5 10 20 30 40 57 and 59 minutes after the intravenous administration of a potassium sparing agent (triamterene or amiloride) or a potent diuretic (ethacrynic acid or furosemide) Then 1 mg of acetylstrophanthidin diluted in 5 c c. of saline was administered into the right atrium over a 15 second period.

Subsequently simultaneous samples from the coronary sinus and femoral artery were obtained at 1 2 4 6 8 12 and 20 minutes after the acetylstrophanthidin Blood samples were replaced with equal volumes of saline All samples were analyzed for sodium and potassium by flame photometry with a Beckman Model DU spectrophotometer and calcium and magnesium by atomic absorption spectrometry with a Perkin Elmer Atomic Absorption Spectrometer

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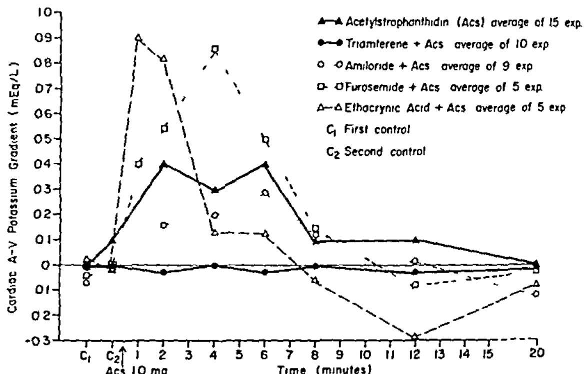


Fig 1 Cardiac A V (coronary sinus femoral artery) potassium gradient (milliequivalents per liter) after acetylstrophanthidin alone and in combination with triamterene amiloride furosemide or ethacrynic acid

Coronary blood flow was determined in two dogs from each group with a Carolina Medical Electronics electromagnetic flowmeter placed on the anterior descending coronary artery

The following groups of animals were studied.

Control group In this group of 15 dogs which did not receive diuretics 1 mg of acetylstrophanthidin diluted in 5 c c of saline was administered into the right atrium [9] Blood pressure and electrocardiograms were monitored

Potassium sparing drug group

Triamterene In this group of 10 dogs 175 mg of triamterene was administered intravenously in divided doses (100 mg initially then three doses of 25 mg at 15 minute intervals) during the 60 minute period prior to the administration of 1 mg of acetylstrophanthidin The triamterene was placed in solution by finely grinding 200 mg of the powdered triamterene in a test tube Then 40 c c of distilled water was added very slowly with continued stirring Lastly, approximately 2 c c of 8 5 per cent lactic acid was added dropwise until the solution became a clear transparent yellow with only minimal amounts of small particles visible to the naked eye The solution was kept warm until injection

Amiloride In this group of nine dogs 1 0 mg per kilogram of amiloride was administered intravenously in divided doses (10 mg one hour before the acetylstrophanthidin and another 10 mg one half hour before the acetylstrophanthidin) during the 60 minute period prior to the administration of 1 mg of acetylstrophanthidin into the right atrium

Potent diuretics

Ethacrynic acid In this group of five dogs 50 mg of ethacrynic acid was administered intravenously one hour prior to the acetylstrophanthidin

Furosemide In this group of five dogs 40 mg of furosemide was administered intravenously one hour prior to the acetylstrophanthidin

Results

All groups The cardiac A V (coronary sinus femoral artery) potassium difference observed during the control period was insignificant (Fig 1)

The rise in femoral artery potassium concentration induced by acetylstrophanthidin as observed by us and by others has been shown to be due to loss of potassium primarily from skeletal muscle and hepatic cells (Tables I through IV) No significant changes were noted in femoral artery or coronary sinus concentrations of sodium calcium or magnesium Coronary flow and blood pressure were relatively constant throughout the study During some arrhythmias, coronary flov

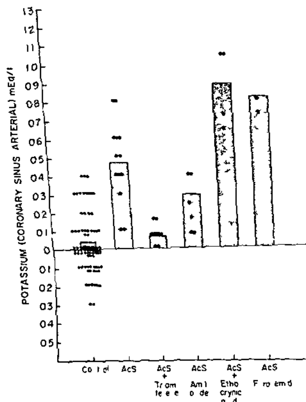


Fig 2 Mean of the maximal differences in potassium concentration (coronary sinus arterial) from 0 to eight minutes (milliequivalents per liter)

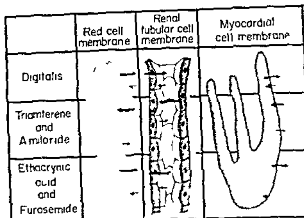


Fig 3 Schematic representation of potassium movement across the red cell membrane renal tubular membrane and myocardial membrane as influenced by digitalis triamterene and amiloride and ethacrynic acid and furosemide Arrows represent movement of potassium across membrane

and blood pressure decreased minimally and transiently but there was no consistent relation to the A V potassium difference

In the *control group* of 15 dogs which did not receive potent diuretics or potassium sparing agents acetylstrophanthidin caused a significant ($p < 0\ 001$) increase in mean maximal cardiac A V potassium difference (coronary sinus femoral artery) of 0 47 mEq per liter which occurred at four to six minutes (Figs 1 and 2) This group was reported previously[9] Arrhythmias developed in seven out of 15 studies (47 per cent) The duration of the arrhythmias averaged 14 minutes

Potassium sparing drug group

Triamterene In this group of 10 dogs which received 175 mg of triamterene prior to the administration of acetylstrophanthidin the cardiac A V potassium difference was abolished (Figs 1 and 2 Table I) The mean maximal A V difference of potassium (coronary sinus femoral artery) averaged 0 1 mEq per liter which was not statistically significant. Arrhythmias occurred in four out of 10 studies and had a mean duration of 5 5 minutes In addition contrary to what might have been expected after the administration of an antikaliuretic there was a 0 4 mEq per liter mean decrease in arterial serum potassium levels This occurred one hour after the administration of triamterene alone and before the administration of acetylstrophanthidin This suggests that the drug may have promoted an intracellular migration of potassium

Amiloride In this group of nine dogs when amiloride (1 0 mg per kilogram) was infused prior to the administration of acetylstrophanthidin the A V potassium difference was reduced but to a lesser degree than observed with triamterene (Fig 1 Table II) The mean maximal A V potassium difference was 0 38 mEq per liter which was not statistically different from that observed with acetylstrophanthidin alone (Fig 2) Arrhythmias occurred in four out of nine studies and had a mean duration of 12 3 minutes

Potent diuretics

Ethacrynic acid In these five studies the intravenous administration of 50 mg of ethacrynic acid prior to the administration of acetylstrophanthidin markedly increased the A V difference of myocardial potassium as compared with that induced by acetylstrophanthidin alone (Fig 1) The mean maximal A V potassium difference was 1 14 mEq per liter This was significantly greater than that observed with acetylstrophanthidin alone ($p < 0\ 01$) (Fig 2 Table

Table I Myocardial potassium (mEq /L) gradient after triamterene and then acetylstrophanthidin

Date	3 11 70			3 18 70			3 18 70			3 25 70			4 1 70		
Min.	CS *	A †	C.S −A	C.S	A	C.S. −A	C.S.	A	C.S −A	C.S	A	C.S. −A	C.S	A	C.S. −A
C1	3 9	3 9	0	4 0	4 0	0	3 0	3 0	0	3 4	3 4	0	4 0	4 0	0
C2	4 0	4 0	0	4 0	4 0	0	3 0	3 0	0	3 3	3 3	0	4 0	4 0	0
Triamterene 100 mg intravenously then triamterene 25 mg at 15 minute intervals, x3															
15	4 0	4 0	0	4 1	4 1	0	3 0	3 0	0	3 7	3 7	0	3 3	3 3	0
30	4 0	4 0	0	4 1	4 2	−0 1	2 0	2 0	0	3 7	3 6	0 1	3 2	3 3	− 1
57	3 6	3 6	0	4 0	4 0	0	2 0	2 0	0	2 9	2 9	0	3 0	3 0	0
59	3 6	3 6	0	4 0	4 0	0	2 0	2 0	0	2 9	2 8	0 1	3 0	3 0	0
Acetylstrophanthidin 1 mg in right atrium															
2	4 9	4 9	0	4 5	4 5	0	4 0	3 9	0 1	3 6	3 6	0	4 4	4 3	1
4	4 7	4 8	−0 1	4 6	4 6	0	4 0	4 0	0	4 0	3 9	0 1	3 9	3 9	0
6	4 4	4 4	0	4 4	4 4	0	4 0	4 0	0	4 0	4 0	0	4 2	4 1	1
8	4 4	4 4	0	4 1	4 1	0	4 6	4 6	0	3 6	3 6	0	3 1	3 0	1
12	4 2	4 2	0	4 4	4 3	0 1	4 6	4 6	0	3 6	3 6	0	3 0	3 0	0
20	3 9	3 9	0	4 0	4 0	0	4 0	4 0	0	3 5	3 5	0	3 4	3 4	0
	No arrhythmia			No arrhythmia			A V dissociation at 3 minutes lasting 10 minutes			Atrial fibrillation at 2 minutes lasting 8 minutes			Nodal tachycardia at 8 minutes lasting 1 minute		

C S Serum potassium (mEq /L) from coronary sinus sample
†A − Serum potassium (mEq /L) from femoral artery sample

III) Arrhythmias occurred in four out of five studies

Furosemide In the five studies in which furosemide was administered prior to the acetylstrophanthidin a marked increase in cardiac A V potassium difference similar to that observed with ethacrynic acid was observed (Fig 1 Table IV) The mean maximal potassium A V difference was 0 98 mEq per liter double that observed with acetylstrophanthidin alone (Fig 2) This was significantly greater than that observed with acetylstrophanthidin alone ($p < 0\ 05$) Arrhythmias occurred in all five studies

In the ten studies where ethacrynic acid or furosemide was administered prior to the acetyl strophanthidin the maximal A V potassium difference and the arrhythmias (nine out of ten studies) usually occurred within one to two minutes after the administration of acetylstrophanthidin The nine arrhythmias had a mean duration of greater than 17 minutes In the 19 studies with triamterene and amiloride maximal cardiac A V potassium difference occurred later and the arrhythmias (eight out of 19) started later These arrhythmias were briefer and had a mean duration of nine minutes

Discussion

As mentioned previously, the coronary blood flow measured in two studies in each group was relatively constant Under conditions of unchanging coronary flow, we believe that the cardiac A V potassium difference reflects egress of potassium from cardiac tissue These experiments suggest that the cardiac effect of triamterene and amiloride reduces the digitalis induced egress of myocardial potassium while furosemide and ethacrynic acid amplify this potassium loss

Although triamterene abolished and amiloride reduced the digitalis induced increase in cardiac A V potassium difference, arrhythmias still developed We believe that this was due to the large (1 mg) pharmacologic dose of acetylstrophanthidin administered In other studies reported elsewhere we have shown that triamterene and amiloride extend the arrhythmogenic dose of acetylstrophanthidin by 110 per cent [10]

Prior studies have shown that diuretics modify potassium transport in the renal tubule and erythrocytes [11-13] Our findings of a cardiac effect of these drugs support the premise that there may be common enzyme systems responsible for potassium transport across the renal tubular membrane, the red cell membrane, and the myocardial membrane De Azevedo and coworkers[5] in our laboratories have shown that amiloride antagonizes certain cardiac electrophysiologic effects of digitalis particularly the latter's effect on maximal rate of depolarization

4 8 70			*4 8 70*			*8 19 70*			*8 26 70*			*8 26 70*		
C S	*A*	*C S −A*	*C S*	*A*	*C S −A*	*C S*	*A*	*C S −A*	*C S*	*A*	*C S −A*	*C S*	*A*	*C S −A*
4 1	4 1	0	3 5	3 6	−0 1	4 0	4 0	0	4 0	4 0	0	3 0	3 0	0
4 1	4 1	0	3 5	3 6	−0 1	4 0	4 0	0	4 0	4 0	0	3 0	3 0	0
4 0	4 0	0	3 6	3 5	0 1	4 0	4 0	0	4 0	4 0	0	3 0	3 0	0
4 0	3 9	1	3 [illegible]	3 6	−0 1	3 9	3 9	0	4 1	4 0	0 1	3 0	3 0	0
4 3	4 3	0	3 0	3 0	0									
4 1	4 1	0	3 0	3 0	0									
4 7	4 7	0	3 1	3 1	0	5 1	5 0	0 1	4 5	4 3	0 2	3 4	3 6	−0 2
4 7	4 7	0	3 1	3 0	0 1	4 0	4 0	0	4 1	4 2	−0 1	3 6	3 6	0
4 3	4 3	0	3 0	3 0	0	4 6	4 6	0	4 1	4 0	0 1	3 6	3 4	0 2
4 1	4 1	0	3 0	3 0	0	4 0	4 0	0	4 0	4 0	0	3 0	3 1	−0 1
5 0	5 0	0	3 0	2 9	0 1	4 0	4 0	0	4 0	4 0	0	3 1	3 0	0 1
5 0	5 0	0	3 0	2 9	0 1	4 0	4 0	0	4 0	4 0	0	3 0	3 0	0
No arrhythmia			No arrhythmia			No arrhythmia			No arrhythmia			A V dissociation at 7 minutes lasting 3 minutes		

and ventricular fiber action potential duration Triamterene and amiloride block renal sodium potassium exchange due to a distal tubular site of action[6,8] Triamterene has also been shown to stimulate both sodium potassium dependent and sodium potassium independent red cell membrane ATPase[4] In contrast ethacrynic acid a potent diuretic due to its renal tubular site of action[14] has been shown to inhibit the digitalis independent sodium potassium dependent membrane ATPase so called Pump II[3,15] Pump II has been described in studies on the red cell membrane It is possible that Pump II" or a similar mechanism may also be present in the myocardial membrane There are probably multiple mechanisms responsible for the transport of potassium back into the myocardial cell One which is digitalis sensitive so called sodium potassium dependent ATPase and one which is digitalis insensitive The latter may be similar to Pump II As in the red cell membrane it may also be impeded by ethacrynic acid and possibly furosemide Thus digitalis and these potent diuretics may have additive blocking action with regard to re entry of potassium into the myocardial cell and, therefore possibly the development of arrhythmias (Fig 3)

Other investigators have shown that the administration of potassium sparing drugs such as amiloride and triamterene protect animals from the so called steroid myocardiopathy[16,17] These investigators attributed the protective value of these drugs to the production of hyperkalemia Our studies suggest that there is also a myocardial effect of these potassium sparing agents which may directly prevent the loss of potassium from the myocardium, thought to underlie the development of steroid myocardiopathy

Conclusions

These studies have shown that several potent diuretic agents have a myocardial site of action Ethacrynic acid and furosemide potentiate the digitalis induced increase in cardiac A V potassium difference and presumably the myocardial potassium egress while potassium sparing agents such as triamterene or amiloride abolish or reduce this effect

The results of these studies suggest that the clinical administration of antikaliuretic agents such as triamterene and amiloride may prevent the arrhythmias of digitalis toxicity not only by reducing kaliuresis and subsequent hypokalemia but also by a myocardial effect which antagonizes the loss of myocardial potassium On the other hand, potent diuretics may facilitate digitalis arrhythmias through a myocardial effect which causes a greater egress of myocardial potassium This may explain the occasional development of lethal arrhythmias immediately

Table II Myocardial potassium (mEq /L) gradient after amiloride and then acetylstrophanthidin

Date	9 3 69			9 18 69			9 25 69			12 10 69		
Min.	*CS **	*A†*	*CS −A*	*CS.*	*A*	*CS −A*	*CS*	*A*	*CS −A*	*CS.*	*A*	*CS. −A*
C1	3 9	3 9	0	4 3	4 2	0 1	4 0	4 0	0	4 0	4 0	0
C2	3 8	3 8	0	4 3	4 2	0 1	4 1	4 0	0 1	4 0	4 0	0
Amiloride 10 mg intravenously then 10 mg intravenously at 30 minutes												
5	3 8	3 8	0	4 5	4 4	0 1	4 1	4 0	0 1			
15	3 4	3 5	−0 1	4 1	4 0	0 1	4 1	4 1	0	3 8	4 0	−0 2
45	3 4	3 5	−0 1	3 7	3 7	0	4 0	4 0	0	5 4	4 7	0 7
57	3 3	3 5	−0 2	3 5	3 7	−0 2	4 0	4 0	0	5 0	4 7	0 3
59	3 4	3 5	−0 1	3 5	3 6	−0 1	4 0	3 9	0 1	5 0	4 7	0 3
Acetylstrophanthidin 1 mg in right atrium												
2	4 7	4 7	0	5 0	4 9	0 1	5 2	5 1	0 1			
4	4 7	4 7	0	4 8	4 7	0 1	5 1	5 1	0	5 5	5 0	0 5
6	4 6	4 6	0	4 7	4 6	0 1	4 8	4 7	0 1	5 6	5 4	0 2
8	4 6	4 7	−0 1	4 6	4 5	0 1	4 6	4 6	0	5 4	5 3	0 1
12	4 5	4 5	0	4 5	4 4	0 1	4 4	4 3	0 1	5 0	5 0	0
20	4 4	4 4	0	4 4	4 4	0	4 1	4 1	0	5 2	5 4	−0 2
	No arrhythmia			No arrhythmia			No arrhythmia			A V dissociation at 3 minutes lasting 12 minutes		

*CS Serum potassium (mEq /L) from coronary sinus sample
†A – Serum potassium (mEq /L) from femoral artery sample

Table III Cardial potassium (mEq /L) gradient after ethacrynic acid and then acetylstrophanthidin

Date	5 6 70			5 13 70			5 20 70			5 27 70			6 3 70		
Min.	*CS **	*A†*	*CS −A*	*CS*	*A*	*CS −A*	*CS*	*A*	*CS. −A*	*CS*	*A*	*CS −A*	*CS.*	*A*	*CS. −A*
C1	3 9	4 0	0 1	3 6	3 3	0 3	3 2	3 2	0	4 0	4 0	0	5 4	5 5	−0 1
C2	4 0	4 0	0	3 7	3 9	−0 2	3 2	3 4	−0 2	4 0	4 0	0	5.5	5 5	0
Ethacrynic acid 50 mg intravenously															
5	4 1	4 0	0 1	4 0	3 6	0 4	4 0	3 9	0 1	4 0	4 2	−0 2	4 5	4 5	0
10	4 0	4 1	−0 1	3 4	3 5	−0 1	4 0	4 0	0	4 0	4 1	−0 1	4 6	4 6	0
20	4 0	3 9	0 1	4 0	4 0	0	4 0	4 0	0	4 0	4 0	0	4 6	4 5	0 1
30	3 9	3 9	0	3 6	3 3	0 3	4 0	4 0	0	4 0	3 9	0 1	4 6	4 6	0
40	4 0	4 0	0	4 0	3 9	0 1	3 4	3 4	0	4 0	3 9	0 1	4 5	4 6	−0 1
41	3 7	4 0	−0 3	3 3	3 3	0	3 6	3 5	0 1	4 0	3 9	0 1	4 6	4 6	0
Acetylstrophanthidin 1 mg in right atrium															
1	5 5	4 4	0 1							5 8	4 5	1 3	6 0	4 6	1 4
2	5 6	4 3	1 3	6 0	5 1	0 9	5 0	4 2	0 8	5 9	5 4	0 5	6 0	5 4	0 6
4	5 0	5 0	0	5 8	5 6	0 2	5 0	5 1	−0 1	6 0	5 4	0 6	5 6	5 6	0
6	4 6	4 6	0	5 6	5 7	−0 1	5 0	4 7	0 3	6 0	5 6	0 4	5 5	5 5	0
8	4 2	4 4	−0 2	5 1	5 1	0	4 7	4 6	0 1	5 1	5 4	−0 3	5 6	5 5	0 1
12	4 1	4 2	−0 1	4 6	4 3	0 3	4 6	4 0	0 6	4 5	5 9	−1 4	4 7	5 6	−0 9
20	4 1	4 1	0	4 0	4 0	0	4 0	4 0	0	4 2	4 5	−0 3	4 7	4 8	−0 1
	Ventricular tachy cardia onset at 30 seconds lasting 15 minutes			A V dissociation onset at 15 sec onds lasting 13 minutes			No arrhythmia			A V dissociation onset at 1 minute lasting 20 minutes			Nodal tachycardia onset at 4 min utes lasting 16 minutes		

*CS – Serum potassium (mEq /L) from coronary sinus sample
†A – Serum potassium (mEq /L) from femoral artery sample

10 16 69			*1 14 70*			*4 22 70*			*4 29 70*			*4 29 70*		
C.S	*A*	*C.S −A*	*C.S*	*A*	*C.S −A*	*C.S.*	*A*	*C.S −A*	*C.S*	*A*	*C.S −A*	*C.S*	*A*	*C.S. −A*
4 0	4 0	0	4 0	4 0	0	4 1	4 0	0 1	4 1	4 0	0 1	3 6	4 0	−0 4
4 0	4 0	0	4 0	4 0	0	4 1	4 1	0	4 0	3 9	0 1	4 0	4 0	0
4 0	4 0	0	4 0	4 0	0				4 0	4 0	0	4 0	3 6	0 4
3 8	3 7	0 1	4 0	4 0	0	5 3	5 0	0 3	3 0	3 3	−0 3	4 0	4 0	0
3 4	3 7	−0 3	4 0	4 0	0	4 9	4 9	0	3 3	3 0	0 3	3 6	4 0	−0 4
3 4	3 7	−0 3	4 0	4 1	−0 1	4 1	4 1	0	3 9	4 0	−0 1	4 0	4 0	0
3 6	3 7	−0 1	4 0	4 1	−0 1	4 4	4 4	0	3 8	3 8	0	3 9	4 0	−0 1
4 0	3 7	0 3	5 0	5 2	−0 2	4 4	4 4	0	5 1	4 8	0 3	5 6	4 5	1 1
4 0	3 7	0 3	5 2	5 2	0	4 0	4 0	0	5 0	4 7	0 3	5 6	4 8	0 6
4 0	3 7	0 3	5 3	4 7	0 6	4 6	4 4	0 2	5 0	4 7	0 3	5 6	5 0	0 6
3 7	3 7	0	5 0	4 6	0 4	4 4	4 4	0	4 5	4 0	0 5	5 1	5 0	0 1
3 7	3 7	0	5 2	5 2	0	4 0	4 1	−0 1	4 0	4 0	0	5 0	5 0	0
3 8	3 7	0 1	5 1	5 1	0	4 0	4 0	0	4 1	4 0	0	4 0	5 0	−1 0
No arrhythmia			A V dissociation at 3 minutes lasting 12 minutes			No arrhythmia			Nodal tachycardia at 2 minutes lasting 15 minutes			A V dissociation at 3 minutes lasting 10 minutes		

Table IV Myocardial potassium (mEq /L) gradient after furosemide and then acetylstrophanthidin

Date	*7 14 70*			*7 20 70*			*7 22 70*			*7 27 70*			*7 29 70*		
Min.	*C.S*	*A†*	*C.S. −A*	*C.S*	*A*	*C.S −A*	*C.S*	*A*	*C.S −A*	*C.S*	*A*	*C.S −A*	*C.S*	*A*	*C.S −A*
C1	4 0	4 0	0	3 0	3 0	0	3 6	3 7	−0 1	3 3	3 0	0 3	4 1	4 0	0 1
C2	4 0	4 0	0	3 0	3 0	0	3 0	3 4	−0 4	3 0	3 0	0	3 0	3 0	0
Furosemide 40 mg intravenously															
5	4 0	3 9	0 1	3 3	3 2	0 1	3 0	3 0	0	3 0	3 0	0	4 1	4 0	0 1
10	4 0	4 0	0	3 6	3 1	0 5	3 1	3 3	−0 2	3 0	3 3	−0 3	4 0	4 0	0
20	4 0	4 0													
30	3 8	3 9	−0 1	3 1	3 3	−0 2	3 0	3 0	0	3 0	3 0	0	4 0	4 0	0
40	3 8	3 8	0	3 0	3 3	−0 3	3 0	2 9	0 1	3 1	3 1	0	4 0	4 0	0
41	3 8	3 8	0	3 1	3 1	0	2 9	3 0	−0 1	3 0	3 0	0	4 0	3 9	0 1
Acetylstrophanthidin, 1 mg in right atrium.															
1	4 0	4 0	0	4 1	3 6	0 5	4 0	3 1	0 9	3 0	3 0	0	4 6	4 0	0 6
2	4 0	4 0	0	4 3	4 0	0 3	4 7	3 3	1 4	4 0	3 1	0 9	4 1	4 0	0 1
4	5 0	4 0	1 0	4 6	3 7	0 6	4 6	3 1	1 5	4 5	3 3	1 2	4 0	4 0	0
6	4 0	4 0	0	4 1	3 6	0 5	4 1	4 1	1 0	4 5	3 6	0 9	4 1	4 0	0 1
8	3 9	4 0	−0 1	4 0	4 0	0	3 7	3 0	0 7	3 1	3 0	0 1	3 9	3 9	0
12	3 9	4 1	−0 2	3 9	4 0	−0 1	3 0	3 0	0	3 1	3 2	−0 1	4 0	4 0	0
20	4 0	4 1	−0 1	4 0	4 0	0	3 0	3 0	0	3 0	3 0	0	3 9	3 9	0
	A V dissociation onset at 30 seconds lasting 17 ½ minutes			Nodal tachycardia onset at 30 seconds lasting 15 minutes			Nodal tachycardia onset at 2 minutes lasting > 20 minutes			A V dissociation onset at 1 minute lasting > 20 minutes			Ventricular tachycardia onset at 2 minutes lasting 8 minutes		

C.S Serum potass um (mEq /L) from coro ary s nus sample
†A Serum potass m (mEq /L) from femo l rtery sampl

after the administration of these potent diuretics despite normal serum potassium levels[18]

As a result of these studies we suggest that potent diuretics be used cautiously especially when given intravenously to patients receiving digitalis In addition the potassium sparing agents, such as triamterene may be helpful in the prevention of digitalis arrhythmias in patients receiving diuretics and digitalis not only by preventing hypokalemia but by reducing the loss of potassium from the myocardial tissue

Summary

Triamterene amiloride ethacrynic acid and furosemide were studied to determine whether they modified the digitalis induced egress of myocardial potassium which is thought to facilitate the development of digitalis arrhythmias In a control group of 15 dogs potassium was measured in samples obtained simultaneously from the femoral artery (FA) and the coronary sinus (CS) in a control period and at intervals after the administration of 1 mg of acetylstrophanthidin Acetylstrophanthidin caused a significant increase in cardiac A V difference in the potassium concentration (CS FA) averaging 0 47 mEq per liter In a group of 10 dogs when 175 mg of triamterene was infused prior to the acetylstrophanthidin the rise in A V difference was abolished and the arrhythmias often aborted In contrast the infusion of potent diuretics (40 mg of furosemide in five dogs and 100 mg of ethacrynic acid in another five dogs) prior to acetylstrophanthidin caused a doubling of the maximal A V potassium difference This study suggests that the clinical administration of antikaliuretic drugs may prevent the arrhythmias of digitalis toxicity not only by reducing kaliuresis and subsequent hypokalemia but by a myocardial effect which antagonizes the digitalis induced loss of myocardial potassium Contrariwise potent diuretics may facilitate digitalis arrhythmias through a myocardial action causing a greater egress of myocardial potassium thus explaining the development of arrhythmias despite normal serum potassium levels These potent diuretics should be used cautiously, especially when given intravenously to patients receiving digitalis.

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Case reports

Disorders of impulse conduction and impulse formation caused by hyperkalemia in man

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Using an experimental dog model we have shown with the aid of His bundle recordings that acutely induced hyperkalemia can produce disturbances of impulse conduction at several levels in the sinoatrial (S A) atrioventricular (A V) and intraventricular conduction system either simultaneously or sequentially [1] Furthermore any of these conduction disorders may be associated with or followed by abnormal regular or irregular ectopic impulse formation The purpo e of this report is to demonstrate simi lar phenomena in eight patients with severe hy perkalemia In two patients the nature of the dis order of rhythm could be classified only by the use of His bundle recordings In the others it could be surmised on the basis of pre existent or transient typical electrocardiographic (ECG) features

Case reports and analyses of ECG s

Case 1 A 15 year-old boy with acute glomerulonephritis developed multiple conduction disorders during advanced hyperkalemia (Fig 1) On March 31 during sinus rhythm *in tra atrial slowing* of conduction was evidenced by flattened and broaden d P waves An additional first degree A V block accounted for prolongation of the P R interval to 0 28 sec a *bilateral interventricular* conduction disorder involving the bundle branch system was indicated by the pattern of right bundle branch block and a frontal axis of about −60 the lat ter compatible with left anterior fascicular block In tramural intraventricular conduction delay was suggested by the extreme QRS prolongation to 0 ?0 sec Serum potassium (K) at this tim was 8 8 mEq per liter On April 1 after peritoneal dialysis serum K fell to 5 5 mEq per liter and all conduction defects regressed but some residual hy perkalemia could be inferred from the presence of peaked symmetrical T wav s

Case 2 Several ECG s obtained in a 63 year old man ad mitted for hemoptysis showed sinus rhythm with a P R inter val *of 0 18 sec* and a left anterior fascicular block (QRS 0 12 sec) (Fig 2 left) During an epi ode of renal failure the pa tient developed severe hyperkalemia (K = 9 1 mEq per liter) ECG s recorded at that time (Fig 2 right) showed a regular ventricular rhythm the origin of which could not be determined P waves were not discernible Multiple intra *ventricular* conduction defects were now evident The QRS had the contour of right bundle branch block with marked right axis deviation consistent with additional block in the *left po terior fasci ular system* Furthermore intramural block was suggested by the increase of QRS duration to 0 20 sec With treatment of the hyperkalemia the ECG reverted back to the original pattern

Case 3 Fig 3 shows two records obtained in a newborn in fant delivered by a patient with eclampsia *The baby died in* severe re piratory distress and had a potassium level of 7 7 mEq per liter An autopsy revealed hyaline membrane dis ease in association with extensive *hemorrhage in the kid* neys The first record on Aug 26 suggested a ventricular tachycardia with its origin in the right ventricle since a pat *tern of left bundle* branch block was present The rhythm was regular at a rate of 125 beats per minute with QRS pro longed to 0 24 sec Atrial activity was not discernible The true nature of the arrhythmia however was revealed by a record taken the next day It showed regular P waves at pre cisely the previous rate of the ventricles with a 2 1 ventricu lar response With this reduction of the ventricular rate to one half the QRS widening was no longer present A pro longed Q T interval and the typical T wave deformation indi cated hypocalcemia in addition to persistent hyperkalemia (K = 7 2 mEq per liter) a combination characteristic of renal failure Thus in retrospect, the first record can be rein terpreted as an atrial tachycardia with extreme aberration of intraventricular *conduction* apparently enhanced by the

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*The terminology for intraventricular conduction disorders follows the recently proposed classification [2]

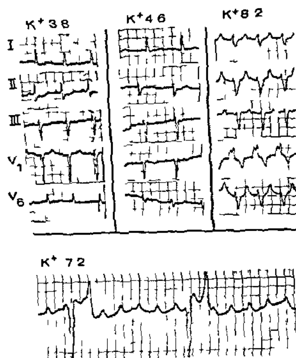


Fig 6 Case 5 Varying areas of block in hyperkalemia No conduction abnormality with serum K at 3 8 mEq per liter Left anterior fascicular block with serum K at 4 6 mEq per liter Right bundle branch and left anterior fascicular block with serum K at 8 2 mEq per liter On another occasion a rise of serum K to 7 2 mEq per liter produced complete A V block

of K within the junction remaining as yet unclear [8]

Thomson[9] produced P R prolongation in man with the oral administration of 15 Gm of *potassium* salt daily Others[10] have produced prolongation of A V conduction or second degree A V block with the oral administration of 2 to 10 Gm of KCl They pointed out that recognizable increases in A V conduction time occurred only in patients with some degree of pre existing block One group of investigators[11] found that prolongation of A V conduction was produced by hyperkalemia only in patients with heart failure One case is on record of second degree A V block produced in an infant by the combination of hyperkalemia and hypoxia[12] as exemplified also by case 3 of this report. As a rule however second and higher degrees of A V block are considered to be unusual in noniatrogenic hyperkalemia in man Indeed, in his most recent article Fisch[3] stated that in hyperkalemia due to the disease process and not to administration of K A V block

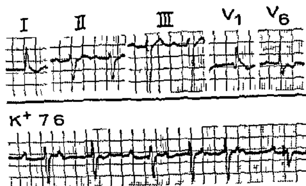


Fig 7 Case 6 Upper panel Pre existent first degree A V block associated with bilateral (right and left anterior fascicular) bundle branch system block Lower panel (Lead III) Second degree A V block during hyperkalemia The last beat of the lower panel is a response to an escaping transvenous demand pacemaker See text

greater than a simple prolongation of P R is yet to be recorded Although our case 6 may be an exception to the rule a markedly advanced degree of A V block may be obscured in the surface ECG by the disappearance of P waves [13] In some advanced A V block may be the result of a trifascicular intraventricular block as presented in our case 5 (Fig 6) In case 7 studied by us during hyperkalemia with His bundle electrography the delay of A V conduction could be localized within the A V node

Intraventricular block QRS prolongation with hyperkalemia was noted at least 40 years ago[14] and it has been considered unlikely that this is due to block within the specialized conduction system alone [13,15] In dogs a progressive increase in QRS duration occurs during slow infusion of potassium chloride [16] Surawicz[17] has stated that as a rule advanced hyperkalemia is characterized by uniform QRS widening resembling a normal QRS complex recorded at a rapid speed. However in other cases the QRS complexes may display fascicular block [18] or resemble bundle branch block[2,3,12] as in our case 2 In this respect it is of interest that in all our cases of intraventricular conduction delay with or without a bundle branch block pattern the QRS was extremely prolonged to 0 18 to 0 20 sec or more Also the fact that slurring and prolongation was seen in the initial as well as terminal inscription of the QRS is an indication that the delay of intraventricular impulse propagation involved not only the bundle branch system but also the con

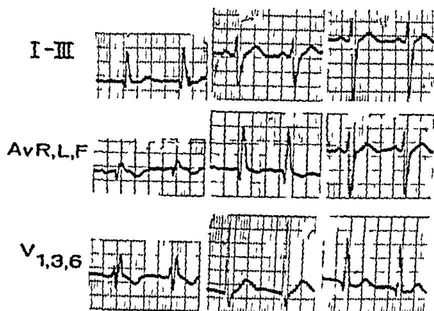


Fig 4 Case 4 Bifascicular bundle branch system block before hyperkalemia

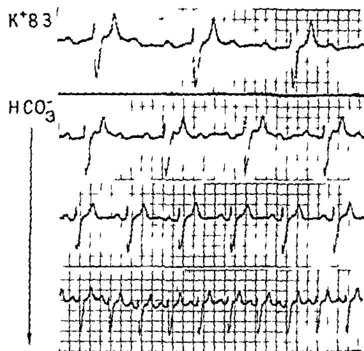


Fig 5 Case 4 Lead aV$_F$ of the same patient as in Fig 4 Additional multiple conduction defects during hyperkalemia regressing gradually as a result of bicarbonate infusion See text

sinoventricular rhythm and in favor of an isorhythmic A V dissociation caused by (1) slowing of the atrial rate due to depressed impulse formation in the sinus node or a second degree S A block and (2) acceleration of a subsidiary probably A V junctional pacemaker

Carotid sinus pressure (Fig 13) produced no change in ventricular rate and rhythm when serum K was 6 5 mEq per liter (upper strip) After reduction of serum K to 4 0 mEq per liter during a junctional rate of 55 per minute sinus P waves gradually emerged leading to persistent capture of the ventricles at a rate of 68 and a P R interval of 0 24 sec without any change in the shape of the ventricular complex (middle strip) Carotid sinus pressure applied at this time (lowest strip) reduced the sinus rate and permitted junctional escape but at a much slower rate (36 per minute) than during hyperkalemia When carotid sinus pressure was released junctional rhythm persisted for two beats at an increased rate Finally the ventricles were once again captured by the sinus pacemaker (last beat)

Discussion

Hyperkalemia is known to affect adversely impulse propagation throughout the heart and to alter the site and sequence of impulse generation The electrophysiologic background of such disorders recently reviewed and summarized by Fisch [3] is beyond the scope of the present communication Our report is an attempt to categorize disorders of impulse formation and conduction observed electrocardiographically in several clinical settings associated with advanced hyperkalemia and to compare them with experimentally derived findings

A V conduction Slowing of the heart rate was produced experimentally with high concentrations of a potassium salt as early as 1906 and 1911 [4,5] It was recognized, without the aid of the ECG, that hyperkalemia could slow the sinus pacemaker as well as produce heart block Fisch and his associates[6,7] reported that many different ECG manifestations of A V block had been produced quite regularly in animals by rapid infusion of potassium salts and that 'the major effect of K is a direct depression of the A V junctional tissue with the exact site of action

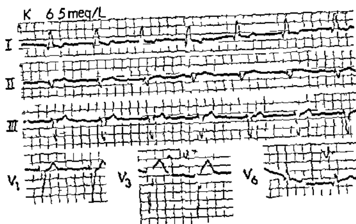


Fig 10 Case 8 Old anterolateral wall infarction with intraventricular (left anterior fascicular and mural) conduction defect *The rhythm is undetermined* See text

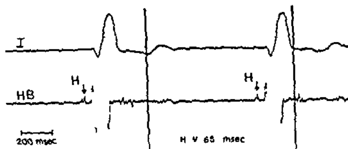


Fig 11 Case 8 Lead I and His bundle recording (*HB*) at 100 mm *paper speed. Time lines at 1 sec intervals* Atrial deflections cannot be identified His bundle potentials (*H*) precede each QRS at an H V interval of 65 msec See text

rhythm is present at a time when no P waves are detectable in the surface ECG[1,19,20] This determination can also be achieved in patients by recording simultaneously or separately atrial and His bundle potentials and their relation to ventricular complexes (Figs 12 and 13) However in man the distinction between various degrees of sinoatrial block and slowing with irregularities of impulse formation within sinus node cannot be made so long as the sinus node potential cannot be established with certainty by intracardiac ECG s

Parasympathetic tone and hyperkalemia Our case 8 showed failure during hyperkalemia of both an accelerated junctional pacemaker and a dissociated sinus pacemaker to slow in response to repeated application of carotid sinus massage Sinus and junctional pacemakers returned to their normal relationships and responses within 15 minutes after potassium was reduced to normal levels. An explanation for these findings might be found in experimental data suggesting an antagonistic effect between hyperkalemia and parasympathetic stimulation Thus hyperkalemia has been shown to increase the sinus rate[21] and the amount of acetylcholine required to produce slowing or arrest of the S A node in animals[22,23] In addition the ability of acetylcholine to produce A V block was inhibited when serum K was infused into vagotomized dogs[24] Finally after administration of morphine and during right atrial pacing the second degree A V block noted to occur with each inspiration was prevented by the infusion of an isotonic solution of potassium into the femoral vein[25] or into the left coronary artery[26]

Summary

In eight patients we have demonstrated manifold types of impairment of impulse conduction produced by hyperkalemia These abnormalities of impulse conduction occurred either si

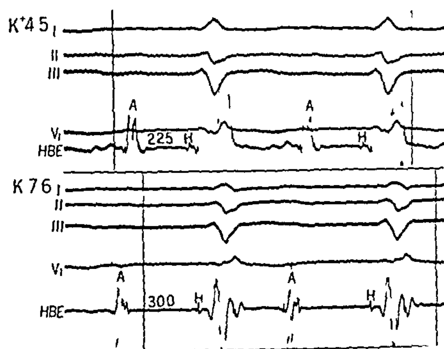


Fig 8 His bundle recordings in case 6 Upper panel Before hyperkalemia A H interval 225 msec H V interval 30 msec Lower panel During hyperkalemia The A H interval prolonged to 300 msec H V interval unchanged See text

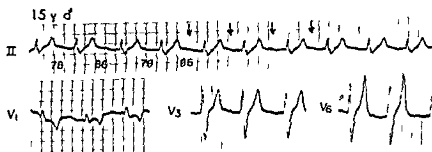


Fig 9 Case 7 Atrial (and ventricular) bigeminy with first degree A V block in hyperkalemia (see text) Arrows in Lead II point to P waves The numbers are P P intervals in hundredths of a second

tracting nonspecific myocardium Finally it appears that hyperkalemia tends to aggravate or add additional delays to any pre existent conduction abnormalities for second degree or complete A V block was always preceded by some type of bundle branch or fascicular block (cases 4 to 6, Figs 4 to 7)

Intra atrial or sinoatrial block and disorders of impulse formation The distinction between conduction disorders in the atria during persistent sinus activity (sinoventricular rhythm) and activation of the ventricles by ectopic impulses[6,7] becomes difficult and often impossible when the P waves become broad, small and even disappear as a result of hyperkalemia This difficulty is compounded when a severe intraventricular conduction defect develops simultaneously (Fig 2) But even when such abnormal P waves can be identified in the standard ECG and related to every ventricular complex any irregularity of their rhythm raises the problem of distinction between disorders of propagation of a regular sinus pacemaker (sinoatrial block) and ectopic impulse formation within the atria as exemplified in Fig 9 Surawicz[17] found that ectopic pacemaker activity is uncommon at serum levels of potassium between 5 5 and 7 5 mEq per liter Fisch agrees[3] that ectopic rhythms are rare in spontaneous clinical hyperkalemia except as a manifestation of a terminal event We found previously however that atrial and ventricular ectopic beats may be a transient event in hyperkalemia associated with hypoxia[12] In addition in the present study we observed transitory acceleration of junctional impulse formation in one patient (case 8)

In animal experiments one can determine by intracardiac or epicardial recordings from atria and ventricles whether a sinoventricular

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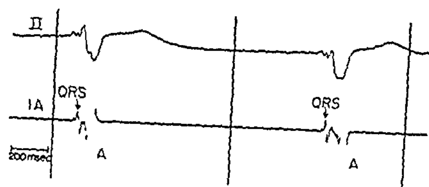


Fig 12 Case 8 Lead II and intra atrial lead (*IA*) Paper speed of 100 mm per second Time lines are at 1 sec intervals The large atrial electrograms (*A*) follow the ventricular potentials (*QRS*) at different intervals See text.

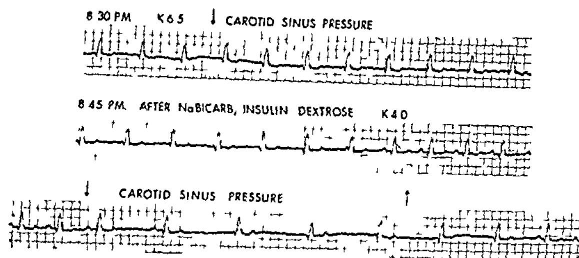


Fig 13 Case 8 Lead I Rhythm during and after correction of hyperkalemia (see text) Downward arrows indicate start and upward arrow release of carotid sinus pressure (no carotid sinus pressure in the middle strip)

multaneously or in sequence and were located in the atria in the A V junction in the fascicular distribution of the ventricular conduction system or in the free ventricular walls In association with the abnormalities of conduction abnormal impulse formation was also frequently observed as manifested by acceleration of normal pacemakers or the emergence of ectopic pacemakers In one patient hyperkalemia produced alteration in sinus and A V junctional impulse formation which overshadowed conduction disorders In all of the eight cases the hyperkalemia was considered to be noniatrogenic

Hyperkalemia appears to potentiate subclinical conduction abnormalities especially in the His Purkinje system However the presence of pre existent intraventricular conduction defects such as a bifascicular block does not exclude the possibility that the site of an A V conduction delay during hyperkalemia can be in the A V node as demonstrated by His bundle recording in one instance after development of second degree (type I) A V block

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Nonocclusive coronary disease after chronic exposure to nitrates Evidence for physiologic nitrate dependence

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Chronic industrial exposure to organic nitrates has been associated with symptoms of chronic nitrate intoxication[1-6] and an increased incidence of deaths caused by coronary artery disease[7] Lange and associates[8] recently described non atheromatous ischemic heart disease that oc curred in workers manufacturing explosives after withdrawal from chronic industrial ex posure to nitroglycerin This report describes a similar syndrome in a young man whose ex posure was limited to the routine handling of ex plosives in his job as an explosives expert, and delineates his improvement after removal from exposure

Case report

A 38 year old mining explosives foreman entered the Veterans Administration Hospital San Francisco with a three month history of recurrent chest pain He was a healthy vigorous and athletic man who had experienced daily exposure for more than 10 years to dynamite "sticks and nitroglycerin gelly His symptoms were consistent with those of heavy exposure to nitrates intermittent nausea pal pitations chronic powder headache[4,9] and pain in the hands upon exposure to cold Continuous daily exposure to nitrates was interrupted in December 1972 and Jan 5 1973 while at home he developed sudden severe crushing substernal chest pain radiating to the left arm associated with nausea and diaphoresis He was admitted to a commu nity hospital where physical examination routine laboratory tests and serial electrocardiographic and cardiac enzyme studies were normal He was treated with analgesics and dis charged after five days without further pain

Several weeks later he began to have recurring attacks of similar pain once or twice a week always while at rest and usually on weekends or Monday mornings The pain was relieved by sublingual nitroglycerin by entering the "powder magazine or occasionally by exercise His work was usually interrupted only briefly and he continued to be able to do heavy lifting and vigorous exercise Persistence of pain prompted referral to the Veterans Administration Hospital Family members were all long lived and there was no history of hyperlipidemia diabetes or heart disease He consumed 10 to 20 aspirins 10 to 15 cups of coffee and two packages of cigarettes daily

Examination revealed a well built (5 feet 11 inches 163 pounds) man appearing younger than his stated age Blood pressure was 100/50 mm Hg pulse was 50 beats per minute respirations were 14 per minute and temperature was 98 6 F The remainder of the examination including the car diovascular system was normal Laboratory data revealed a hemoglobin of 12 9 Gm per 100 ml hematocrit reading of 36 9 per cent, and a white blood cell count of 9 600 per cubic millimeter with a normal differential count. Results of the following tests were normal or negative urinalysis chest roentgenogram serum total protein albumin globulin bilirubin glutamic oxaloacetic transaminase lactic dehydrogenase fasting glucose creatine phosphokinase uric acid alkaline phosphatase sodium potassium chloride bicarbonate cholesterol (201 and 239 mg per 100 ml) triglycerides (105 and 130 mg per 100 ml) calcium phosphorus blood urea nitrogen creatinine plasma prothrombin time partial thromboplastin time arterial blood gases blood methemoglobin level (0 9 per cent) 24 hour creatinine clearance erythrocyte sedimentation rate electrocardiogram (Fig 1 panel *A*) and oxygen/hemoglobin affinity (P_{50} = 24 1 mm Hg normal 25 1 ± 0 9 mm Hg)

On the fourth hospital day exercise electrocardiography was done After 15 minutes on a treadmill the patient achieved the fifth grade of exerci e (5 m p h 18 per cent grade) with a maximum heart rate of 180 beats per minute (blood pressure 160/70 mm Hg) There were no ST segment changes on the electrocardiogram at any time during or after the test

Selective right and left coronary arteriography and left ventricular angiography were done on the fifth ho pital day Initial injections into the left coronary circulation showed no abnormalities (Fig 2 upper panels) however just before in jection into the right coronary artery the patient developed substernal chest pain. Injection of contrast material revealed spasm in the midportion of the right coronary artery (Fig 2

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lower left panel) which, along with the pain disappeared after sublingual nitroglycerin (Fig 2 lower right panel) No electrocardiographic changes were noted during the pro cedure and the left ventricular angiogram and left ventricu lar end diastolic pressure were normal The patient had six more attacks of pain during the next three hours They were not associated with significant electrocardiographic changes (Fig 1) and each was relieved by the administration of sublingual nitroglycerin The frequency of recurrences prompted the use of isosorbide dinitrate which, when given every 60 to 90 minutes prevented the pain Persistent headache necessitated discontinuing the isosorbide dinitrate 24 hours later Serial enzyme and electrocardiographic stud ies were normal The patient returned to full ambulation over the next five days without the recurrence of pain. He was dis charged with instructions to take nitroglycerin as needed and to change his occupation.

One year later he reports that attacks of pain have decreased in frequency (now one or two per month) and se verity he continues to lead an active life as a construction foreman and to pursue vigorous leisure activities without restriction.

Discussion

Organic nitrate explosives are commercially available as dynamite sticks consisting of 20 to 80 per cent nitroglycerin and ethylene glycol dinitrate and as nitroglycerin gelly a similar explosive with a pliable base and a higher ratio of ethylene glycol dinitrate to nitroglycerin In most areas where dynamite is manufactured by open methods or where large amounts of nitrates are stored, there are high levels of nitrates in the air [5 6 10 11] These volatile compounds are readily absorbed through the lungs and skin and are ac tive in extremely small quantities The phar macologic effects of nitrates often seen in per sons who work in such areas include drowsiness vertigo parasthesias headache palpitations dyspnea abdominal pain anorexia nausea vomiting and polyuria [1 5 9] Prolonged exposure results in signs of hypotension tachycardia pe ripheral vasodilation cyanosis dermatitis gastritis peptic ulceration Heinz body positive hemolytic anemia and hepatitis [2 3,5 6 8]

The association of ischemic coronary artery disease and chronic exposure to nitrates is well known[5 7 8 12 14] and has been recently reviewed.[8] The anginal syndrome characteristically occurs in a population screened for the presence of heart disease and with a mean age less than the average for the onset of angina [7] It usually occurs while at rest, on weekends or after periods free from contact with nitrates [7 8 12] It improves in the winter months and may respond to removal from nitrate exposure [8 12] Most patients have a history

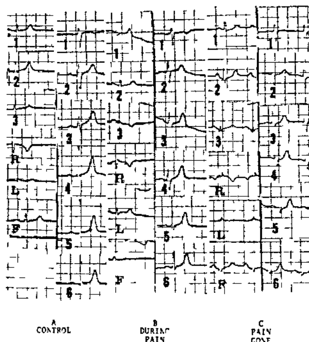


Fig 1 A through C Representative electrocardiograms be fore during and after an attack of chest pain.

of years of exposure and manifest objective evi dence of atheromatous disease [7 8 13] although sud den death often in the absence of preceeding symptoms or demonstrable occlusive coronary disease has occurred.[7,8 13]

These data point to consideration of (1) the re lationship between exposure and the increased incidence of occlusive coronary artery disease in these patients and (2) the relationship between the pharmacologic effects of chronic exposure and of sudden withdrawal from nitrates and symptomatic nonocclusive heart disease The first relationship has been discussed[7] however little data are available from which to draw firm conclusions Our patient and one of Lange and associates[8] do however illustrate that sympto matic nonocclusive heart disease and coronary artery spasm may occur in patients during with drawal from chronic exposure to organic ni trates In these patients it is possible that chronic nitrate exposure may in addition to af fecting the peripheral circulation affect the vascular stability of the coronary circulation This latter concept is supported by the beneficial responses seen in this and other patients when exposure to nitrates is reduced and implies that this process is reversible

Previous studies of nitrate related heart dis

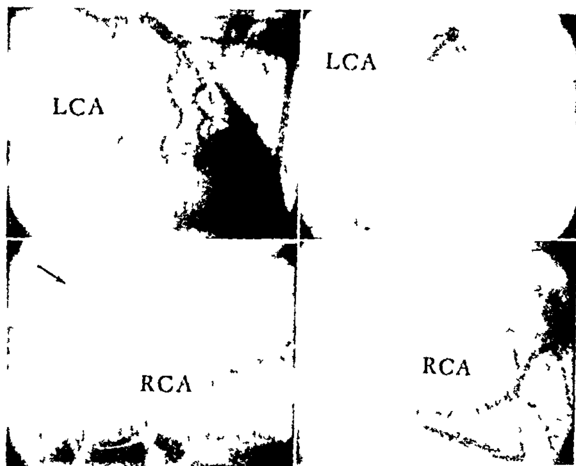


Fig 2 Selective angiograms of the left (LCA) and the right (RCA) coronary arteries showing normal anatomy of the LCA (upper left and right panels) and an area of spasm in the proximal RCA during an attack of chest pain (lower left panel) Resolution of the spasm is seen after sublingual nitroglycerin (lower right panel)

ease have been limited to persons engaged in manufacture of explosives Although he was not engaged in manufacture, this patient was ex posed for many years to large amounts of organic nitrates and he suffered similar symptoms of chronic nitroglycerin intoxication Withdrawal from exposure was temporally associated with the appearance of chest pain clinically indistin guishable from ischemic cardiac pain however it occurred in an apparently healthy man who had few of the known risk factors for coronary disease and who had angiographically normal coronary arteries

Although the risk of industrial exposure has been minimized with the introduction of auto mated manufacture of explosives [11] exposure to commercially available nitrates remains a prob lem Therefore until the risk of exposure from these products is reduced, it would seem wise to remove from exposure those patients who dem onstrate signs or symptoms of chronic nitrate in toxication or symptomatic heart disease

Summary

A 38 year old man exposed to nitroglycerin in his work as an explosives expert developed non occlusive ischemic heart disease after with drawal of exposure to organic nitrates Despite the severity of his symptoms and the documented spasm of his right coronary artery his elec trocardiogram was at all times normal as were results of a wide panel of laboratory tests Sublin gual nitroglycerin ameliorated the symptoms which have decreased with time

I thank Dr A B Willeford for referring this patient and Dr Charles F Reinhardt E. I Dupont Nemours & Co for his consultations Dr Thomas Bradley performed the oxygen/hemoglobin affinity test and Dr Harold W March performed the selective arteriography and left ventricular angiography

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Clinical pathologic conference

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Laura Knight M D
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DR WILLIAM A NEAL. The male infant was the product of a 40 week gestation, uncomplicated pregnancy and delivery The birth weight was 8 pounds 8 ounces and Apgar score at 1 minute was 7 Color and cry were described as ' normal upon arrival in the nursery but, by 10 hours of age the infant was noted to be dusky when crying and was not tolerating feedings

At two days of age he was transferred to the University of Minnesota newborn intensive care unit. He was deeply cyanotic and respirations were mildly labored The heart rate was 160 per minute, respiratory rate 80 per minute and simultaneous upper and lower extremity flush blood pressures were 48 mm Hg Examination of the head and neck was negative The lungs were clear to auscultation The first and second heart sounds were single and prominent third and fourth heart sounds were audible There was no cardiac murmur The liver was palpable 5 cm below the right costal margin Peripheral pulses were of normal intensity and there was no edema

Blood gases were drawn through an umbilical artery catheter while the infant was breathing 100 per cent ambient oxygen in a head box pH was 7 41 PCO_2 24 mm Hg and PO_2 24 mm Hg Blood glucose calcium, sodium and potassium were normal Hemoglobin was 22 4 Gm per cent and hematocrit 74 per cent. Urinalysis showed 1+ protein and occasional red blood cells An electrocardiogram performed the day of admission was interpreted as showing a pre excitation pattern variant of Wolff Parkinson White syndrome (Fig 1)

Dr Knight will you comment on the patient's thoracic roentgenogram?

DR LAURA KNIGHT Pulmonary vascularity is markedly decreased There is moderate cardiomegaly and a slightly prominent right cardiac border No parenchymal infiltrates are identified (Fig 2) Ebstein s anomaly would have to be considered however the heart is not as large as is usually seen in this condition The findings are consistent with tricuspid atresia or perhaps pulmonary atresia

DR NEAL Thank you Dr Knight I would like to call upon Dr Bessinger to discuss the clinical findings

DR F BLANTON BESSINGER When faced with a cyanotic, newborn infant a sense of urgency exists because of concern that the hypoxia present will lead rapidly to acidosis and deterioration Congenital heart disease is often first incriminated as a cause of cyanosis but the cyanotic infant must be approached with the knowledge of other causes of cyanosis These include polycythemia, sepsis hypoglycemia shock central nervous system disease cooling pulmonary disease and persistent fetal pulmonary vascular resistance with temporary right to left shunting at the atrial and/or ductal level When these causes are ruled out even then cardiac disease has to be considered with a question Is the cyanosis primary or secondary? An example of the latter would be cyanosis seen in an infant in marked congestive cardiac failure with pulmonary

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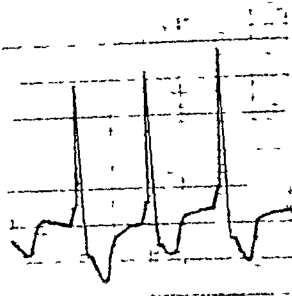


Fig 1 Lead V_2 of electrocardiogram showing delta wave suggestive of Wolff Parkinson White pre excitation pattern



Fig 2 Thoracic roentgenogram in frontal view

edema and poor perfusion The primary type of cyanosis would be due then to congenital cardiac anomalies resulting in admixture of venous and arterial blood or anomalies resulting in decreased pulmonary blood flow and entry of systemic venous blood return into the systemic arterial circulation Examples of lesions in the admixture group would be transposition of the great arteries single ventricle and truncus arteriosus The lesions with decreased pulmonary blood flow are generally described as having tetrad physiology and include tetralogy of Fallot, pulmonary atresia with intact ventricular septum hypoplastic right ventricle tricuspid atresia and Ebstein s malformation of the tricuspid valve

The important finding in this infant is the presence of cyanosis I presume since birth The time of onset of cyanosis is an important point in differential diagnosis. The appearance of cyanosis several days after birth suggests the onset of congestive cardiac failure shock or other problems Cyanosis from birth suggests that the problem is congenital cardiac disease but this certainly does not exclude other causes Other important physical findings are (1) normal heart rate (2) tachypnea (3) normal blood pressures in the arm and leg (4) auscultatory findings of a single second heart sound, presence of third and fourth heart sounds and absence of a murmur and (5) hepatomegaly No comment was made on the quality of perfusion or the degree of distress of the infant

The thoracic roentgenogram is an integral part of any evaluation of the cyanotic infant This patient s film demonstrates cardiomegaly with a prominent right atrial border and decreased pulmonary vascular markings

In this patient cyanotic congenital cardiac disease is the most likely etiology of the child s condition As a cause of the cyanosis the roentgenographic finding of decreased pulmonary vascular markings is against consideration of a left sided obstructive lesion with attendant increased pulmonary venous pressure and is against an admixture lesion usually associated with increased pulmonary blood flow A normal blood pressure also tends to rule out coarctation of the aorta Therefore we are led to a consideration of a lesion with tetrad physiology The presence of cardiomegaly hepatomegaly and tachypnea suggests congestive cardiac failure This negates the consideration of the tetralogy of Fallot however the diagnosis of congestive cardiac failure is tenuous in the presence of a normal cardiac rate What has to be remembered is that these signs of congestive failure may reflect other problems i e tachypnea secondary to hypoxia and hepato

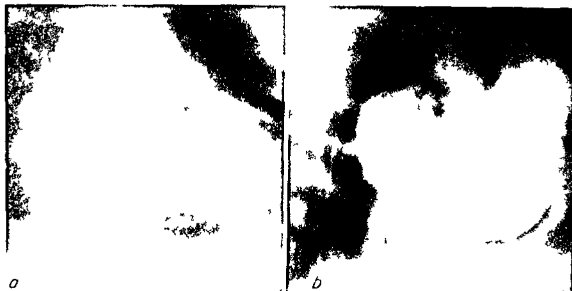


Fig 3 Right atriogram *A* frontal view *B* lateral view

megaly secondary to obstruction of venous return Thus, cardiomegaly in association with decreased pulmonary markings is suggestive of Ebstein s malformation, tricuspid atresia, or pulmonary atresia with an intact ventricular septum

The auscultatory finding of a single second heart sound is not helpful in that it would be compatible with any of these latter lesions The quadruple' rhythm present suggests Ebstein s anomaly however, third and fourth heart sounds could be present in any child with a poorly functioning ventricle or with resistance to ventricular filling The absence of a cardiac murmur favors tricuspid atresia or pulmonary atresia over Ebstein s anomaly but the presence or absence of a murmur in neonatal cardiac disease has not been particularly helpful in differential diagnosis of the acutely ill patient The electrocardiogram shows an axis of +75 degrees and a pattern suggestive of Wolff Parkinson White syndrome The mean frontal plane axis certainly fits more with pulmonary atresia or Ebstein s anomaly than with tricuspid atresia The presence of Wolff Parkinson White syndrome has been described in many types of cardiac disease but would statistically be more likely in Ebstein s malformation or tricuspid atresia

Thus, by a process of elimination, Ebstein's anomaly must be considered as the No 1 diagnosis Other causes of obstruction to blood flow into through or out of the right ventricle have not been ruled out

If the infant has not shown clinical improvement cardiac catheterization should be performed to establish a definite diagnosis A surgical procedure to affect an increase in pulmonary blood flow may need to be considered.

Dr Neal The infant was digitalized with Lanoxin, 0 05 mg per kilogram as the total digitalizing dose Over the next 12 hours however, his condition worsened despite further treatment of congestive cardiac failure with diuretics and respiratory assistance Right sided cardiac catheterization was attempted It was not possible to advance the catheter into the right ventricle and a right atriogram was performed. This was followed by a Rashkind procedure (balloon atrial septostomy) without noticeable improvement in the infant s condition He was taken to the operating room and a Waterston shunt (ascending aorta right pulmonary artery anastomosis) and atrial septectomy under inflow occlusion were performed Postoperatively the patient s course was complicated by focal seizures arrhythmias and renal failure One week later he died

Dr Knight will you show the angiograms?

Dr Knight· Contrast material is injected into an enlarged right atrium (Fig 3) There is almost immediate opacification of an enlarged left atrium followed by opacification of the left ventricle and aorta The bodies of the right ventricle right ventricular outflow tract and pulmonary artery are not visualized In two frames of the frontal projection there appears to be a trickle of contrast material in the inflow portion of the right ventricle In the lateral view there is a suggestion of a lobulated filling defect in the right atrium which is not seen in the frontal compan

ion films These findings are consistent with marked stenosis of the tricuspid valve A mass in the right atrium such as a tumor cannot be ruled out

DR NEAL Dr Bessinger would you care to comment on the cardiac catheterization findings and the infant s subsequent course in the hospi tal?

DR BESSINGER The catheterization findings lead to a diagnosis of tricuspid atresia The course of the catheter is abnormal in that it does not enter the right ventricle The right atrio gram demonstrates massive shunting of blood from right atrium to left atrium There is the pe culiar finding of the narrow band of contrast ma terial in what appeared to be the right ventricle At the time of catheterization this was not ade quately explained. It appeared that the child s problem was obstruction of systemic venous re turn at the level of the tricuspid valve There was no apparent ventricular septal defect which would aid in filling of the pulmonary arterial tree from the left ventricle Thus a shunt procedure was in order A Waterston shunt was recom mended and was carried out The atrial septec tomy was performed at the same time to guarantee an exit of blood from the right atrium We have seen several patients with right ventric ular obstructive lesions who have had deteriora tion in their course because we believe of an in adequate atrial septal opening

DR NEAL Dr Blieden will you please describe the necropsy findings?

DR LEONARD C BLIEDEN The significant find ings were confined to the heart brain and kid neys Several subepicardial nodules measuring up to 3 mm in diameter were present on the an terior surface of the heart The right atrium was markedly dilated and its wall thickened The surgically created atrial septal defect was iden tified and appeared to be adequate for right atrial decompression The tricuspid orifice was marked ly obstructed by an irregular rounded tumor mass nearly 2 cm. in diameter which occupied the inferior one third of the right atrium (Fig 4 *A*) The cut surface of the tumor was smooth and pale From the right ventricular aspect, the mass protruded through a normally developed tri cuspid valve and occupied about half of the right ventricular cavity (Fig 4 *B*) The outflow portion of the right ventricle was normal although several smaller tumor nodules studded the ven



Fig 4 *A* interior of right atrium (R A) and tricuspid valve area viewed from above The tricuspid valve is obscured by a large bulbous tumor mass (T) *B* interior of right ventricle (R V) The tumor (T) has presented through the tricuspid orifice into the right ventricle P V = pulmonary valve

tricular myocardium The pulmonary arteries were normal and the surgically created ascend ing aorta right pulmonary arterial anastomosis (Waterston shunt) was patent The left atrium and mitral valve were normal There was mild to moderate subaortic obstruction secondary to a tumor mass in the ventricular septum (Fig 5)

The microscopic appearance of the tumor was typical of rhabdomyoma (Fig 6) Large vacuo lated spaces of irregular size presenting a spongy appearance suggestive of atypical Purkinje cells were present

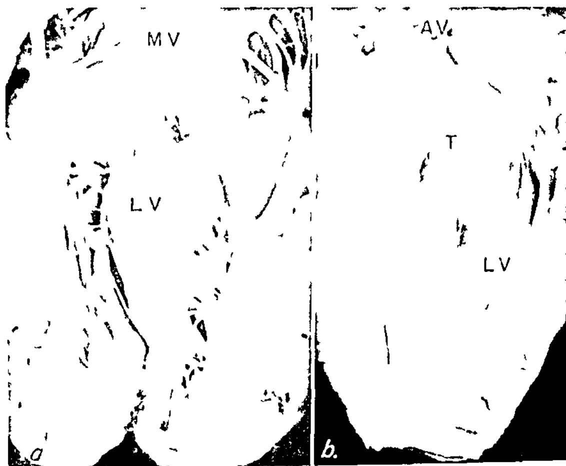


Fig 5 *A* left ventricle (L V) and mitral valve (M V) Several small tumor nodules are evident in the ventricular septum *B* outflow portion of left ventricle (L V) and aortic valve (A V) In addition to tumor nodules appearing in the cut surface of the left ventricular wall there is a second large tumor mass (T) in the subaortic area which causes some obstruction



Fig 6 *A* photomicrograph of left ventricular wall The large clear cells represent one of the tumor nodules in the left ventricular wall Hematoxylin and eosin ×85 *B* photomicrograph of the tumor mass obstructing the tricuspid orifice It is composed of large clear cells typical of congenital rhabdomyoma Hematoxylin and eosin ×340

In addition to the cardiac findings, the cut surface of the kidneys revealed multiple cystic lesions up to 5 mm in diameter a condition sometimes associated with congenital rhabdomyoma Examination of the brain demonstrated scattered, firm nodules composed of giant astrocytes over the cerebral cortex and similar lesions extending from the subependymal area into the lateral ventricles These lesions were characteristic of tuberous sclerosis which has been seen in approximately 50 per cent of infants dying with congenital rhabdomyoma of the heart

DR NEAL Dr Edwards would you discuss the pathologic findings which have been present?

DR JESSE E EDWARDS Congenital rhabdomyoma is not considered a malignant tumor but is associated with a very poor prognosis In one series of 69 cases only 15 per cent of the patients lived beyond 5 years of age [1] Death usually results from complications of tuberous sclerosis arrhythmia or mechanical interference with cardiac function Right and/or left ventricular outflow obstruction has been frequently referred to in the literature but, to my knowledge there has been only one previous reference to rhabdomyoma completely obstructing the tricuspid valve This occurred in a six month old female infant with tuberous sclerosis [2]

The case presented showed the typical pathologic changes of congenital rhabdomyoma of the heart This was characterized by multiple myocardial nodules one of which was dominant as to size

There are a few reports of other types of primary and secondary tumors causing tricuspid obstruction Sterns and associates [3] in a review of intracavitary neoplasms reported the case of a 54 year old diabetic male with Kimmelsteil Wilson syndrome who at necropsy was found to have a right atrial myxoma obstructing the tricuspid orifice Similar hemodynamic impairment has been caused by a right ventricular fibroma [4] and by a metastatic leiomyosarcoma of the inferior vena cava [5] and by extension of bronchiogenic carcinoma into the superior vena cava and right atrium.

DR NEAL Dr Bessinger in view of the unexpected and interesting condition found in this patient would you care to make some closing remarks?

DR BESSINGER The presence of cyanosis and roentgenographic evidence of decreased pulmonary blood flow in a newborn suggests a number of possible diagnoses most of which are serious forms of congenital cardiac disease The least serious problem would have been persistence of fetal vasculature normally a benign transitory condition not associated with cardiomegaly or congestive cardiac failure The initial clinical impression regarding our patient was that Ebstein s anomaly was present This was suggested by the presence of third and fourth heart sounds a prominent right atrial shadow in the roentgenogram and an electrocardiographic pattern of a Wolff Parkinson White variant However against this diagnosis was the steadily deteriorating condition during the first 48 hours of life Usually newborns with Ebstein s anomaly, if symptomatic at all tend to improve as pulmonary vascular resistance falls Therefore a right sided obstructive lesion such as tricuspid or pulmonary atresia was considered most likely The right atriogram showing no egress of blood into the right ventricle was wrongly interpreted as diagnostic of tricuspid atresia and palliative surgical procedures appropriate for that condition were performed

Retrospectively, it is evident that the angiogram shows a scalloped appearance of the tricuspid orifice and a faint rim of contrast material outlines the margin of the mass lesion as it bulges into the right ventricle In addition arrhythmias and a pre excitation pattern on the electrocardiogram though uncommon in tricuspid atresia are frequently encountered in cardiac tumors in infancy

Accurate antemortem diagnosis of cardiac tumors is often difficult as is typified in this case Echocardiography is very promising as an adjunctive aid in the detection of cardiac tumors and we have successfully diagnosed congenital rhabdomyoma in one infant by this method [6] Greater diagnostic accuracy will not only allow some patients with resectable cardiac tumors to be benefited by surgery but may prevent surgical therapy for those patients who are not likely to benefit from it

FINAL DIAGNOSIS Congenital rhabdomyoma of the heart simulating tricuspid atresia

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Quantification pitfalls in comparative studies of antianginal therapies

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Angina is a difficult phenomenon to quantify but since medical and surgical treatments of angina exist and are constantly undergoing improvements there is a definite need to quantify angina as precisely as possible in order to reduce the number of patients and the length of observation required to reach statistically significant conclusions and thus make antianginal trials feasible and not unduly costly

The purpose of this paper is to review some of the seldom mentioned precautions required to make valid conclusions about the effects of medical and surgical therapies on the basis of subjective and objective information

Subjective quantification of angina

The subjective quantification of angina is littered with biases of different origin but they must be controlled and coped with because they contain clinically pertinent information Rarely can a single investigator find a sufficient group (i e n = 30) of patients with a stable form of angina instability with the passage of time increases experimental error and requires long treatment periods 6 to 12 weeks per treatment at the very least. The stimuli required to elicit angina in everyday life are uncontrollable a situation which often invalidates the medical significance attached to the mere recording of the number of attacks and constitutes the most important source of bias in angina questionnaires can one ascribe to a drug a 50 per cent reduction in attack frequency when its administration coincides with a summer vacation? Only in patients with stable stimuli (emotional and environmental) does the attack frequency give valid information on the angina threshold Furthermore these stimuli are difficult to measure with any degree of precision by most patients

Even if angina questionnaires of increasing sophistication are developed and used, the self evaluation of the intensity and duration of each attack remains unreliable to some degree and the resulting scores should at best be considered qualitative or semiquantitative Comparable remarks apply to the functional classification of the American Heart Association* this ranking scale of measurement has the advantage of being easy to standardize between medical centers but presents the disadvantage of being insufficiently sensitive for detecting small changes in small samples of patients Another source of imprecision is the placebo response the higher it is the more difficult it becomes for a pharmacological effect to become statistically significant and therefore detectable by a clinical trial Furthermore the placebo response may vary from one patient to another and from one physician to another all within the same trial [1]

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* Class I No limitations of phys al ctivity
Class II Slight l m tation of phys cal activity
Class III Ma ked l m tati n of phys cal activity
Cla IV Inabil ty to carry n any physical act ty

Ratios of attack frequency

Occasionally, the ratio formed by the attack frequency during placebo over the attack frequency during treatment is used to compare different treatments with each other by means of parametric tests (i e , t test of Student or F test of Snedecor) Even if one multiplies the ratio by 100 and obtains a percentage the following remark holds true the application of parametric tests on ratios (or percentages) is not entirely valid Parametric tests assume that the distribution of the ratio follows a symmetrical nearly Gaussian law but one does not need a mathematical 'expose' to understand that both the numerator and the denominator are subject to random fluctuations and that even if both terms follow the bell shaped distribution, the resulting quotient will not [2] For example a given reduction in attack frequency during placebo will lead to a greater increment in the quotient than a given increment of the same magnitude in the attack frequency during treatment.

Means of such ratios cannot therefore be validly contrasted against each other by parametric tests but there are four valid alternatives to circumscribe this problem One is to use a covariance analysis where the variable under study is the attack frequency during treatment and the covariable is the attack frequency during placebo such a procedure allows the cardiologist to answer the question whether the treatment s effect would still be significant if all patients had presented the same frequency of attacks under placebo A second alternative consists in stratifying patients according to frequency of attacks during placebo and carrying out a two way variance analysis These two alternatives will considerably reduce the potential bias which often occurs when patients are not matched according to severity of angina [3] A third valid alternative consists in using parametric tests on the logarithm of the quotients a procedure that tends to minimize the asymmetrical distribution mentioned above Brantmark and associates[4] recently published a therapeutic trial of lidoflazine in angina where all statistical analyses were validly done on the logarithm of the quotient

$$\frac{\text{Attack frequency during placebo}}{\text{Attack frequency during lidoflazine}}$$

A final alternative is to use distribution free nonparametric tests of medians such as the ranking tests of Wilcoxon, Mann Whithney, etc [5] Aronow and colleagues[6] recently used the Wilcoxon rank sum test to compare exercise performance between two groups of patients[6] this test is less sensitive but more valid than a t test and its generalized use would increase the validity of antianginal trial reports

Nitroglycerin consumption

A quantitative variable such as the number of nitroglycerin tablets consumed, must be linearly related to the phenomenon under study (i e severity of angina) to be considered a valid estimation of what it purports to measure and this relation must hold irrespective of the experimental conditions (i e treated or untreated) or severity of the anginal state (i e Grade II or III) Nitroglycerin consumption is often used by clinical pharmacologists as a measure of the severity and frequency of anginal attacks it appears as 'harder data because it can more easily be counted than the softer data obtained by scoring the attacks as light moderate and severe

Fig 1 illustrates data from a therapeutic trial of oxprenolol vs placebo conducted by Wilson and colleagues Expectedly, the number of nitroglycerin tablets was highly correlated with the number of anginal attacks in both groups of patients (p < 0 01) However the slope of the regression of the number of tablets over the number of attacks was flatter in the placebo group (b = 0 59) than in the oxprenolol group (b = 0 76) Nitroglycerin consumption exhibits a tendency to level off when the frequency of attacks becomes too large These authors explain this phenomenon Patients limited their intake of glyceryl trinitrate for two reasons they objected to taking too many tablets and the headache following glyceryl trinitrate was often unpleasant This self imposed restriction in nitroglycerin consumption introduced a measurement bias by underestimating the efficacy of oxyprenolol in patients subject to very frequent attacks Wilson and colleagues[7] conclude that The number of glyceryl trinitrate tablets frequently did not reflect the condition of the patient ' Nitroglycerin consumption should consequently be considered as semi quantitative ranking data and should be analyzed by nonparametric tests

A pharmacological bias not to be overlooked either is that resulting from possible deteriora

tion of the tablets potency after remaining several months in opened or plastic containers[8]

Objective quantification of angina

Serial exercise testing with the properly designed test protocol[9] remains the method of choice for comparing antianginal treatments

The proper choice of an exercise test procedure varies markedly with the primary objectives of the observers utilizing it These included (1) detection of myocardial ischemia for diagnosis purpose (2) assessment of functional capacity and (3) repetitive testing for serial observations and longitudinal assessment of individual changes under the influence of the effects of medical and/or surgical therapy It is our purpose to deal primarily with the third objective

Treadmill tests Although a treadmill test intended mainly for comparison of antianginal treatments should retain a reasonable degree of specificity and sensitivity its most valuable asset should be discriminacy The discriminating power of a method is usually expressed as the smallest true difference that is expected to be detected say 95 out of a hundred times Because there is no way to make sure that a given patient will be twice in the same physiological and psychological condition the discriminacy* of exercise protocols cannot be evaluated statistically at the present time A priori however the most valuable version should be the one where the rate of application of the workload is relatively slow permitting the measurement of performance criteria to be repeated after smaller increments in workload. It also lowers the probability of having to stop the exercise for extracardiac reasons such as fatigue leg pain etc Redwood and colleagues[10,11] have insisted on the choice of a progressive workload, especially on the need of allowing the patient to exercise for at least three minutes before angina occurs during the placebo period They also demonstrated that the use of low initial loads and slow rates of workload increments do not alter the end points We currently use a constant treadmill speed of 3 m p h and a 2 5 per cent increment in grade every three minutes when such tests are repeated on three separate days during the same week the reproducibility is satisfactory as illustrated in Fig 2

*These authors use sensitivity for the property that we hereby describe as discriminacy

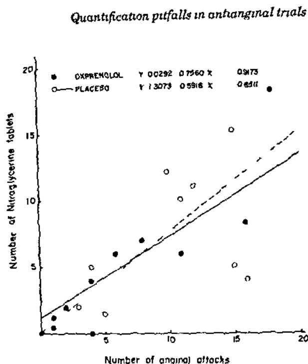


Fig 1 Graphical representation of data from Wilson and colleagues (Br Med J I 155 1969 Reproduced by permission) showing regression of number of nitroglycerin tablets consumed over number of anginal attacks during placebo (*solid line*) and oxprenolol (*discontinuous line*) the latter slope is slightly steeper because patients under placebo had a tendency to limit their nitroglycerin consumption despite higher attack frequency and severity A bias results whereby nitroglycerin consumption underestimates the reduction in angina under the influence of oxprenolol.

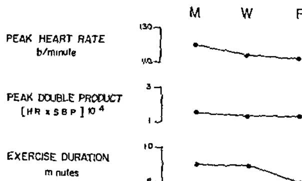


Fig 2 Short term *reproducibility of* three performance criteria mean values measured *in six patients* with positive treadmill tests carried out on three separate *days of* the same week at the same time of the day None of the mean *differences* between days were significant even at the 10 per cent level *No effect* of training was detectable either

Heterogeneity in responsiveness

A seldom discussed source of error that probably occurs oftener than is realized results from a marked *heterogeneity* in responsiveness to a treatment within a supposedly *homogeneous* sample of patients[12] For example some indi

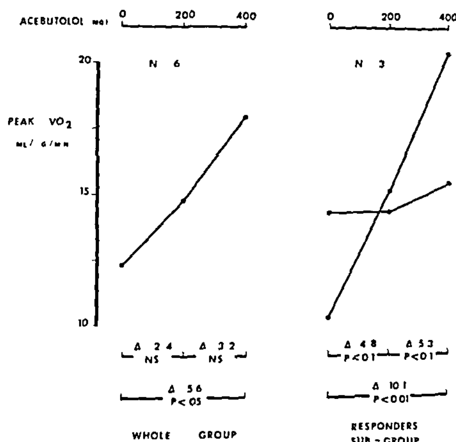


Fig 3 The left side shows the mean values from six patients for peak Vo_2 during a submaximal exercise repeated on three separate days 3 5 hours after a single dose of 0 200 and 400 mg respectively of the new beta blocker acebutolol The mean values resulting from grouping the patients into three responders and three non re sponders are shown on the right side This separation into two categories of responsiveness led to a substantial gain in size and statistical significance of the differences between means in the responders category

viduals may be greatly improved by a given therapy whereas some will scarcely be benefited and a few others may even be made considerably worse Such discrepancies in responsiveness can be known only after completion of the experi ment and can best be appreciated by looking carefully at the raw data

We recently had the opportunity to study in anginal patients the influence of three different single doses of acebutolol (M & B 17803 A, Poulenc Canada) given prior to submaximal treadmill tests conducted on three separate days In the first six patients studied the mean values of five performance criteria were slightly im proved by the drug The left side of Fig 3 shows the results for peak Vo_2 Consideration of indi vidual results however, gave the impression that our small sample was made of three non re sponders and three responders this impression was verified statistically by submitting the data to a split plot variance analysis and finding a sig nificant interaction between treatments and category of responsiveness [3] We then proceeded to a separate analysis of drug effect in each of the two categories and the results appear in the right side of Fig 3 Expectedly the effect of acebutolol on mean values in the responder subgroups was greater and the significance levels attained were larger When present this interac tion points to the existence of two subpopula tions one of responders and one of non re sponders but very large samples are needed to determine the approximate proportion of un selected anginal patients belonging to each of these categories Continuation of this study with a larger sample size subsequently confirmed the efficacy of this new drug

Suppose that 15 patients already tested on a treadmill eventually underwent aortocoronary bypass surgery and that one year postoper atively the tests were repeated Suppose also that all 15 patients were unchanged Analysis of the mean difference by the usual paired t test would lead one to conclude that surgery had a non significant effect However suppose that in another similar study, five patients were im proved five were left unchanged and five were made worse The t test for mean difference would

again reveal a non significant effect and this time such a conclusion would be misleading The three sub groups should be first tested together by split plot analysis for significance of responsiveness × treatment interaction and if this interaction was significant (at say the 20 per cent level) the three categories should be tested separately for treatment effect Then will come the true conclusions that 33 per cent are significantly improved 33 per cent are unchanged, and 33 per cent are made significantly worse The need for post therapeutic stratification has been aptly pointed out by Feinstein[12] as a way of avoiding false negative or false positive conclusions if the patients in different *a posteriori* strata respond in opposite ways to different treatments

Conclusion

There are two types of possible approaches for measuring the essentially subjective phenomenon of angina one consists in gathering soft data through a questionnaire bearing on frequency and severity of attacks nitroglycerin consumption and level of activity possible without reaching angina threshold The resulting qualitative and semi quantitative data are less statistically satisfying than quantitative data derived from objective measurements[5] More patients and longer observation periods are required to detect a treatment effect when there is one This type of data is however clinically very pertinent since it bears on what the patient is interested in namely to see his rate of attacks diminish and to be able to exert himself more without reaching the anginal threshold There is no doubt that soft data collection should continue to receive careful attention in this paper we have recalled the precautions required for making valid statistical evaluation of such subjective information

The objective quantification of angina consists in carrying out a carefully designed submaximal exercise protocol (preferably on a treadmill) and measuring several performance criteria such as VO_2, exercise duration etc reached immediately before the onset of angina or of electrocardiographic signs of ischemia These quantitative criteria are appropriately analyzed with the more powerful parametric methods such as the t test and F test We have brought attention to the choice of the exercise test version most likely to achieve optimum discriminacy and reproducibility and to a statistical precaution required to allow treatment comparisons to remain powerful even when the patients differ markedly in their responsiveness

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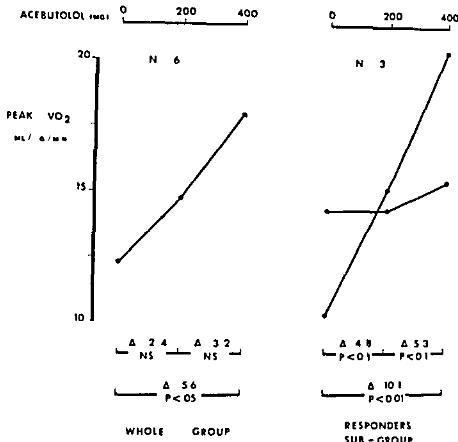


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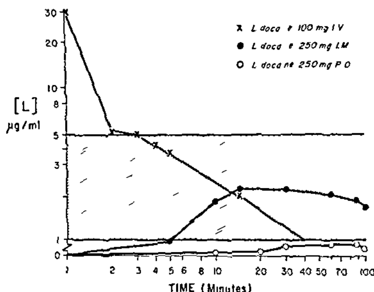


Fig 1 Plasma lidocaine concentrations following administration of single doses intravenously intramuscularly and orally to human subjects Plasma concentration and time both plotted on log scale Shaded area indicates therapeutic concentration range (Modified after Fehmers Van Daatselaar and Dunning [13])

ethylglycine [8,9] The pharmacological effects of these metabolites have not been determined.

The metabolic products are excreted in the urine in man less than 10 per cent of administered lidocaine is excreted unmetabolized.[6,10] As might be expected for a drug so dependent on hepatic metabolism for its degradation in instances of severe heart failure and/or liver disease the plasma clearance of lidocaine is reduced.[11] Hence these clinical situations warrant a decrease in the rate of lidocaine infusion and in total dose to avoid drug toxicity [11,12]

To maintain antiarrhythmic plasma lidocaine levels for prolonged periods following a single intravenous injection infusions of 20 to 50 μg per kilogram per minute are needed [3] If an intravenous infusion is begun without an initial lidocaine injection the attainment of plasma levels sufficient for the termination of arrhythmias is slow For example a 60 to 70 μg per kilogram per minute infusion administered without a prior single lidocaine bolus will not bring plasma concentrations to the therapeutic range for 30 to 50 minutes [4] In instances where a lidocaine injection of 1 mg per kilogram has proved inadequate to control an arrhythmia the dose can be repeated in 3 to 5 minutes However doses in excess of 300 mg should be used with extreme caution because of the likelihood of toxicity [3]

Plasma lidocaine concentrations and the duration of antiarrhythmic effect are not as well documented for intramuscular and oral as they are for intravenous administration Fehmers Van Daatselaar and Dunning[13] reported that following an intramuscular injection of 250 mg of lidocaine plasma concentrations greater than 1 μg per milliliter were attained within 5 to 10 minutes and levels in the 2 μg per milliliter range were reached in 15 to 30 minutes Mean plasma levels of approximately 1 5 μg per milliliter then were maintained for 2 hours (Fig 1)

Studies of oral lidocaine (Fig 1) have indicated that only 35 per cent of the drug is absorbed and that doses of 250 to 500 mg result in plasma concentrations below the therapeutic range [14] A major reason for the ineffectiveness of oral lidocaine may be its rapid metabolism by the liver Once absorbed by the gastrointestinal tract lidocaine passes into the hepatic portal circulation to the liver where approximately 50 per cent may be cleared before the drug enters the systemic circulation [7] Hence following oral ingestion a low plasma level of lidocaine and a high level of one or more metabolites would be expected However there have been reports of lidocaine levels in the therapeutic and toxic ranges following oral administration [15] On the basis of present information it appears that the absorption metabolism, and effects of lidocaine following oral administration are sufficiently unpredictable to contraindi

Electrophysiology and pharmacology of cardiac arrhythmias V Cardiac antiarrhythmic effects of lidocaine

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The local anesthetic lidocaine was synthesized by Lofgren[1] in 1946 and initially administered as a cardiac antiarrhythmic by Southworth and associates[2] in 1950 During the last 15 years the drug has been used increasingly for the emergency treatment of ventricular arrhythmias Lidocaine can be administered rapidly intravenously readily attains antiarrhythmic plasma (and presumably tissue) levels, is rapidly metabolized and excreted and with careful use has limited toxicity These characteristics ideally suit the drug for the short term management of arrhythmias which carry with them the threat of ventricular fibrillation and sudden death or serious impairment of cardiac function

Clinical spectrum of antiarrhythmic activity

Lidocaine primarily is used to treat ventricular premature depolarizations and tachycardia resulting from cardiac disease or digitalis toxicity In different series it has proved satisfactory 70 to 90 per cent of the time[3] Lidocaine is less efficacious in the therapy of supraventricular arrhythmias Forty to 50 per cent of patients with atrial or atrioventricular junctional premature depolarizations or paroxysmal supraventricular tachycardias have been reported to respond well to lidocaine[3] As for the remaining spectrum of supraventricular arrhythmias, lidocaine is even less satisfactory with different investigators reporting its efficacy as being between 0 and 15 per cent[3]

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Clinical pharmacology

Lidocaine usually is administered intravenously, the initial dose being a single injection of approximately 1 mg per kilogram Therapeutic plasma concentrations are 1 or 2 to 5 μg per milliliter[4] If cardiac output is good the initial high plasma lidocaine level (> 30 μg per milliliter) following an intravenous injection immediately begins to fall as the circulating drug equilibrates with such well perfused tissues as the kidneys lungs liver, and heart.[5] Because lidocaine has a high affinity for fat it is also bound readily to adipose tissue[5]

Within approximately ½ minute of lidocaine injection 70 per cent of the drug has left the blood and entered the highly perfused tissues and fat, while less than 1 per cent has been metabolized.[5] As plasma lidocaine levels fall the diffusion gradient from tissue to blood increases and the lidocaine which initially entered the well perfused tissues diffuses back into the blood and is metabolized by the liver The major determinants of the $t_{½}$ of lidocaine (about 30 minutes following an intravenous bolus of 50 to 100 mg) are the distribution of lidocaine in the body and hepatic metabolism the latter being effected largely by microsomal enzymes[6-8] Lidocaine first is de ethylated to form N ethyl or monoethyl glycylxylidide[8,9] This in turn may be cleaved at the amide linkage to form xylidine and N

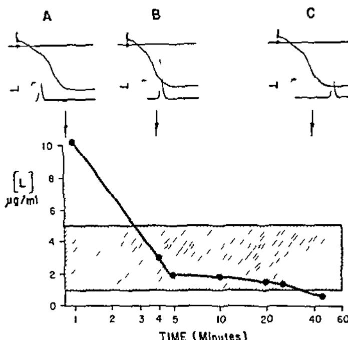


Fig 3 Effect of lidocaine on the Purkinje fiber action potential. In this study lidocaine (1 mg per kilogram) was given as an intravenous bolus to an anesthetized dog The subsequent plasma lidocaine concentrations are depicted in the figure the shaded area indicating the therapeutic concentration range *A* is a control action potential recorded from a Purkinje fiber superfused with the anesthetized dog s blood. The lower trace indicates a 200 V/sec calibration and the $\dot{V}_{max}$ of phase 0 In *B* at a plasma lidocaine concentration of 4 μg per milliliter action potential amplitude V_m and action potential duration all have decreased. In *C* at 0 9 μg per milliliter values for these parameters are approaching control Scale vertical axis 20 mV horizontal 50 msec plasma [K] = 3 9 mM *(Rosen Merker and Pippenger)*

and Davis and Temte[29] indicated that lidocaine had little or no effect on phase 0 depolarization or conduction until rather high concentrations were attained. At these high concentrations (11 to 50 μg per milliliter) they reported that lidocaine decreased action potential amplitude V_{max} and membrane responsiveness Bigger and Mandel[28] also indicated that lidocaine improved conduction across the Purkinje fiber–papillary muscle junction when the drug acted on partly depolarized fibers They proposed that this improved conduction might provide a mechanism for abolishing re entrant arrhythmias through the restoration of normal conduction in critical areas of unidirectional conduction block (Fig 2) However Singh and Vaughan Williams[30] in studies of rabbit atrial and ventricular tissues indicated that lidocaine has only a depressant effect on myocardial action potentials decreasing amplitude and V_{max} (and therefore presumably slowing conduction) in concentrations less than 10 μg per milliliter The extent to which this depressant effect occurred varied with the superfusate [K+] being more prominent as [K+] was increased above 3 mM

A similar depressant effect of lidocaine on the action potential parameters which determine conduction has been described by Rosen Merker and Pippenger[31] In these studies lidocaine was administered intravenously to an anesthetized dog and its effects on the electrophysiologic properties of Purkinje fibers superfused with the dog s arterial blood were observed (Fig 3) Following an intravenous injection of lidocaine (1 mg per kilogram) at plasma concentrations in the therapeutic range (Panel *B*) action potential amplitude and V_{max} were decreased and repolarization was accelerated. As the plasma drug concentration fell below 1 μg per milliliter (*C*) control action potential parameters were again attained. In studies of membrane responsiveness (Fig 4) lidocaine induced a concentration dependent depression of the membrane responsiveness curve (relating V_{max} of phase 0 depolarization to the level of membrane potential at which the action potential is initiated) This depression

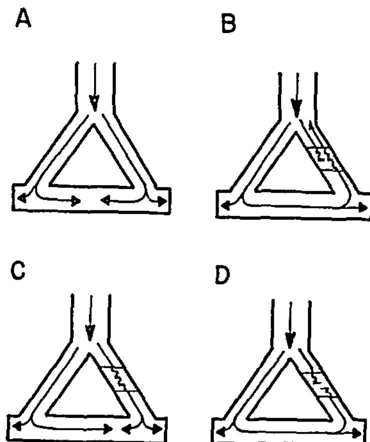


Fig 2 Schematic diagram of re entrant pathway and means for its modification *A* Normal propagation through the distal conducting system to the ventricle Conduction proceeds with equal velocity through both limbs of a terminal Purkinje fiber bundle and then activates the myocardium *B* Shaded area indicates diseased tissue including partially depolarized Purkinje fibers Antegrade activation through the site is blocked *Activation proceeds normally through the* other limb to the myocardium and then activates the *depressed segment in a retrograde direction* This impulse succeeds in propagating slowly through the depressed segment and re enters the proximal conducting system *C* If physiologic changes occur or appropriate pharmacologic agents are administered (see text) conduction may improve through the depressed segment resulting in re establishment of antegrade activation and abolition of re entry *D* If changes occur (or are induced) which result in block of retrograde activation as well as antegrade activation then bidirectional conduction block occurs This condition too would suppress a re entrant arrhythmia

cate its routine clinical use by this route

The most frequent manifestations of lidocaine toxicity occur in the central nervous system and include a spectrum of drowsiness and euphoria through disorientation and convulsions as concentrations increase in the 5 to 10 μg per milliliter range [3] Other symptoms and signs of toxicity include dyspnea dysarthria, blurred vision muscular fasciculations hypotension, respiratory arrest, and death [3,4] Lidocaine toxicity may occur not only after intravenous administration for treatment of cardiac arrhythmias but after its administration as a local anesthetic. For example, following administration of lidocaine during obstetrical anesthesia sufficient drug has been reported to cross the placenta to bring neonatal plasma levels into the toxic range [16] In addition signs and symptoms of toxicity may occur in the mother [17,18] Use of lidocaine during other forms of local anesthesia also may be associated with high plasma levels and toxicity [17,19]

Administration of lidocaine orally is associated with toxic manifestations not seen when the drug is given parenterally Dizziness has been described in volunteers given 500 mg of lidocaine orally[14,20] and emesis has occurred in dogs given oral lidocaine [21] Since these events occur at plasma lidocaine concentrations lower than the usual therapeutic level, they may be due to metabolites which are produced following passage through the liver when the drug is administered orally [14]

Cardiac toxicity is an infrequent accompaniment of lidocaine therapy Although the drug is a myocardial depressant,[22,23] the occurrence of hypotension as a result of lidocaine therapy is rare [3] Isolated instances of lidocaine induced arrhythmias have been reported including conversion of 2 1 to 1 1 atrial flutter sinus arrest, A V block and death [3,24,6] Despite these events lidocaine induced cardiac electrophysiologic toxicity appears to be less frequent than that caused by other antiarrhythmics

Cellular electrophysiologic effects of lidocaine and possible mechanisms of antiarrhythmic action

The therapeutic actions of lidocaine can be explained in part by its effects on conduction refractoriness and automaticity of cardiac fibers. Since the interactions between healthy and diseased fibers in all likelihood, are responsible for arrhythmias drug actions on both types of fibers are important Unfortunately to date studies of the cellular electrophysiologic actions of lidocaine have been performed mainly on normal cardiac tissues

A Effects of resting membrane potential action potential amplitude and phase 0 upstroke velocity (V_{max}) Some of the early reports of lidocaine effect on isolated cardiac tissues have been the source of controversy concerning its mechanism of antiarrhythmic action Studies of normal canine Purkinje fibers by Bigger and Mandel[27,28]

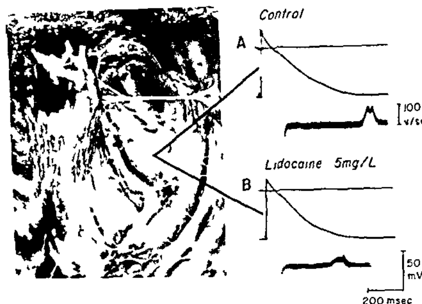


Fig 5 Effects of lidocaine on the action potential of a canine subendocardial Purkinje fiber surviving in a region of extensive myocardial infarction. At the left the infarcted anterior septum from which the action potentials at the right were recorded, is shown. In the panels at the right the top trace is 0 potential the middle trace is the voltage time course of the action potential and the bottom trace is the differentiated upstroke velocity The top panel is the control. The bottom panel shows the effects of 5 mg per liter of lidocaine Note that this concentration of drug decreases the amplitude of the action potential and the rate of depolarization

tial duration and refractory period of fibers at the gate region to a much greater extent than those located proximally or distally (Fig 6) Action potential durations of subendocardial Purkinje fibers at the cardiac apex are so short that lidocaine may exert only minimal effects on their repolarization [37]

Although the decrease of action potential duration induced by lidocaine is accompanied by shortening of the effective refractory period several studies indicate that the refractory period does not decrease as much as the action potential This may be due to a drug induced delay in the reactivation of the sodium carrier responsible for phase 0 [38] As a result after lidocaine administration the earliest premature response arises at a more negative level of membrane potential and conducts at a more rapid velocity than the earliest premature impulse elicited before drug action

The greater effect of lidocaine on action potentials with an initially long duration and refractory period and the lesser effect on action potentials of short duration may contribute to the suppression of re entry We have previously described two mechanisms whereby re entry might result from the occurrence of premature depolarizations and inhomogeneity of action potential duration and refractoriness in the distal Purkinje system (1) re entry may occur when action potential durations and refractory periods at the gates in some regions have been shortened by disease while other regions remain normal (2) re entry may occur in the subendocardial Purkinje fiber network in regions of extensive myocardial infarction [34] Should the differentially greater effect of lidocaine on action potentials of long duration hold true for these situations then lidocaine might decrease the duration of the action potential and refractoriness at the site of longer duration to a greater extent than at the site of shorter duration (Fig 7) This could eliminate the unidirectional conduction block of early premature impulses which initiate re entry Although premature depolarizations still might occur they would be less likely to induce re entry and sustained re entrant tachycardias This hypothesis for a possible mechanism for lidocaine s antiarrhythmic action requires experimental verification.

C Effects on automaticity We have indicated previously that spontaneous impulse initiation may occur by two different automatic mechanisms [39] One occurs at membrane potentials between approximately −90 and −60 mV and is due to a time and voltage dependent decrease in

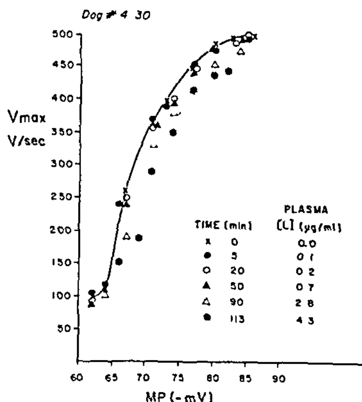


Fig 4 Effects of lidocaine on membrane responsiveness of blood superfused Purkinje fiber In this study an isolated Purkinje fiber bundle was superfused with the blood of an anesthetized dog The control membrane responsiveness curve relating V_{max} of phase 0 to the level of membrane potential at which the action potential was initiated is indicated by the X s A 50 μg per kilogram per minute lidocaine infusion was then given to the donor After 113 minutes at a plasma concentration of 4 3 μg per milliliter the responsiveness curve was depressed Plasma [K] = 4 mM (Rosen Merker and Pippenger)

was seen within the therapeutic plasma concentration range

It is important to note that these changes in the cardiac action potential are concentration dependent and of increasing magnitude as plasma lidocaine concentrations are elevated from the therapeutic to the toxic range It is equally important however to recognize that these changes all are seen initially at clinically therapeutic plasma lidocaine concentrations These studies suggest that in therapeutic situations lidocaine is capable of slowing conduction through its effects on phase 0 depolarization and on membrane responsiveness Lidocaine induced depression of conduction in reentrant pathways theoretically might convert areas of unidirectional conduction block into bidirectional conduction block, thereby abolishing re entry (Fig 2 *D*)

That lidocaine exerts a differential effect on healthy and diseased tissues is suggested by studies of the effects of lidocaine on Purkinje fibers surviving in regions of extensive myocardial infarction[32,33] In such Purkinje fibers, maximum diastolic potential amplitude and V_{max} are reduced and are further depressed by therapeutic concentrations of lidocaine (Fig 5) Lidocaine induced improvement in these transmembrane potentials has not been observed indicating that lidocaine probably does not hyperpolarize cardiac cells which have a decreased resting membrane potential due to ischemia or infarction

As we have discussed previously,[34] re entry in loops of Purkinje fiber bundles and ventricular muscle or in unbranched Purkinje fiber bundles, may be dependent on the occurrence of 'slow response action potentials A weak inward current, distinct from the rapid inward sodium current, is responsible for the depolarization phase of these action potentials[34] A full understanding of the antiarrhythmic effects of lidocaine requires knowledge of its action on these slow responses unfortunately such information is not available at present

B Effects on action potential duration refractoriness and conduction of premature impulses The initiation of re entry and resultant sustained arrhythmias can be the result of premature depolarizations Therefore, it is plausible that antiarrhythmic drugs might exert some therapeutic effects by modifying the conduction of premature impulses Such conduction can be altered not only by the effects of drugs on resting membrane potential, action potential amplitude and V_{max} but by effects on the action potential duration and refractoriness

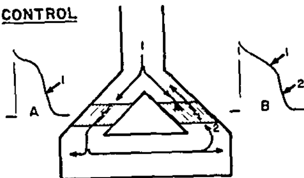
Lidocaine dramatically shortens the action potential duration and effective refractory period of Purkinje fibers[27] The magnitude of this effect varies with the location of the Purkinje fiber within the specialized conducting system[35] As described previously[36] Purkinje fiber action potential duration and refractoriness increase in the peripheral conducting system reaching a maximum at the gate a site several millimeters prior to insertion of the free running strands into ventricular muscle Distal to the gate both parameters decrease The action potential duration of distal subendocardial Purkinje fibers is longest toward the base of the heart and decreases towards the apex Lidocaine causes the greatest changes in action potential duration and refractoriness in normal Purkinje fibers in which these parameters are longest to start with[35] Hence it shortens the action poten

Effects of lidocaine on the in situ heart

The results of both experimental and clinical studies indicate that lidocaine has little effect on sinus rate or on the electrophysiologic properties of the in situ atrium Unlike other antiarrhythmic agents such as quinidine and procaine amide there appears to be little if any modification of autonomic tone by lidocaine The effects of lidocaine on sinus node function in patients with disease of this structure are less certain Reports of sinus arrest after lidocaine administration have appeared in the literature [25] The possibility exists that the diseased or abnormal sinus node is more sensitive than the normal to depressant effects of this drug

The actions of lidocaine on conduction and refractoriness of the A V conduction system have been investigated with the His bundle recording technique [48-50] This method enables drug effects on conduction and refractoriness in the A V node to be distinguished from effects on conduction and refractoriness in the ventricular conducting system At therapeutic plasma concentrations lidocaine has little effect on the electrocardiographic P R interval and on the A H (A V nodal conduction) and H V (His Purkinje conduction) intervals of the His bundle electrogram In some instances intraventricular conduction may be prolonged [49] Lidocaine has a variable effect on A V nodal refractoriness Although pooled data indicate no effect on the A V nodal effective refractory period in some individual cases there is significant shortening while in others refractoriness is slightly prolonged. Shortening of the A V nodal effective refractory period might have some clinical significance in that an increased ventricular rate might result if the drug were given to patients with atrial flutter or fibrillation Lidocaine consistently shortens the effective refractory period of the His Purkinje system in the in situ heart as determined in studies using His bundle recordings and premature atrial stimulation [50] This effect is most likely a reflection of the decreases in action potential duration and effective refractory period of Purkinje fibers described above

Rosen and associates[48] have indicated that in some patients with pre excitation lidocaine prolongs the effective refractory period of the anomalous but not the normal A V conducting pathway These investigators suggested that because of this effect on the bypass tract lidocaine might be efficacious in the therapy of pre excitation



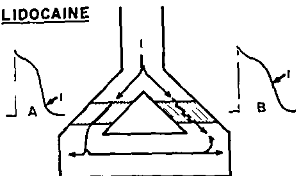


Fig 7 Possible mechanism for elimination of re entry due to premature depolarizations In the "control panel two gates are shown that at *A* having a shorter action potential duration and effective refractory period than that at *B* A premature depolarization propagating through the conducting system arrives before the end of the effective refractory period at *B* (arrow *1*) and is blocked, but after the end of the effective refractory period at *A* due to the more rapid repolarization (arrow *1*) It traverses *A* and activates the distal myocardium arriving in retrograde fashion at site *B* after the end of the effective refractory period (2) It can then traverse *B* and re enter the proximal conducting system In the lidocaine panel the differential effect of this drug on action potential duration has induced a greater degree of shortening at *B* than at *A* As a result the premature impulse (*1*) arrives at both sites *A* and *B* after recovery of excitability Therefore it no longer blocks at *B* but traverses both sites (although *B* more slowly than *A* as the action potential duration here is still longer than at *A*) preventing the occurrence of reentry

Further investigation of this possibility is needed.

Despite the seemingly minor effects of lidocaine on conduction in the normal A V conducting system it must be emphasized that A V nodal disease or disease of the conducting system can modify these actions For example instances of heart block due to lidocaine administration have been reported in patients with an abnormal A V conducting system Josephson and associates[50] described a case of complete heart block induced by lidocaine in which His bundle recordings indicated the site of block to be the A V node Liss

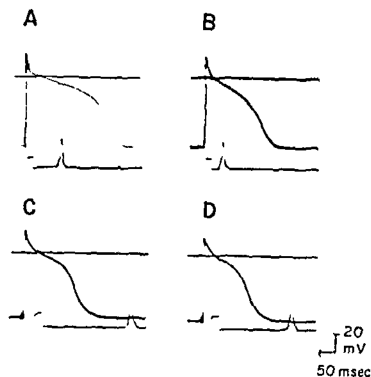


Fig 6 Effects of lidocaine on a Purkinje fiber at the area of maximum action potential duration or gate (*A*) and on a fiber in the more distal conducting system (*C*) Records made during Tyrode superfusion at $[K^+]_o$ = 4 mM *A* and *C* are controls *B* and *D* are records made after 30 minutes of superfusion with lidocaine 2 µg per milliliter Note that at the gate (*A* and *B*) lidocaine has induced a greater degree of shortening of action potential duration than distally (*C* and *D*) (Rosen Merker and Pippenger)

an outward K^+ current (iK_2) The second mechanism for automatic impulse initiation occurs at low levels of membrane potential (< −60 mV) and is associated with slow response action potentials Lidocaine suppresses spontaneous diastolic depolarization and automatic impulse initiation which occurs at membrane potentials between −90 and −60 mV Because this occurs at lidocaine concentrations which do not suppress impulse initiation by the sinus node the function of the latter as the dominant cardiac pacemaker can be restored by lidocaine The effect of lidocaine on spontaneous diastolic depolarization and automaticity due to the mechanism which occurs at low levels of membrane potential (<−60 mV) is uncertain however, preliminary observations indicate that when a membrane potential <−60 mV is due to extensive infarction, the phase 4 depolarization is quite resistant to the effects of lidocaine [40] This finding may explain why some ventricular arrhythmias cannot be abolished by lidocaine [41]

The lesser efficacy of lidocaine in the therapy of atrial, as opposed to ventricular, arrhythmias is explained in part by the observations of Mandel and Bigger [42] In studies of isolated Tyrode superfused rabbit atria they observed that concentrations in excess of 23 µg per milliliter were needed to modify sinus rate and the slope of phase 4 depolarization in sinus node cells and to induce significant decreases in action potential amplitude and V_{max} of atrial specialized conducting fibers These observations indicate a lesser sensitivity of atrial specialized conducting tissues to the cellular electrophysiologic effects of lidocaine than exists in the ventricle

The ionic basis for the cellular electrophysiologic effects of lidocaine

The effects of lidocaine on phase 0 depolarization have been attributed to a decrease in membrane conductance for Na [43] As a result action potential amplitude and V_{max} are decreased However, the magnitude of this effect appears to be less than that for therapeutic concentrations of other antiarrhythmic drugs such as procaine amide [43] The extent to which lidocaine decreases V_{max} is related to cardiac rate as shown by Tritthart Fleckenstein, and Fleckenstein [44] They demonstrated that the magnitude of the depressant effect of lidocaine on V_{max} was increased as stimulus rate was accelerated

Lidocaine alters phase 4 depolarization by changing the outward potassium current which is initiated when repolarization restores membrane voltage to the maximum diastolic potential As previously described phase 4 depolarization in large part depends on a steadily decreasing outward potassium current (iK_2) during phase 4 [45] Lidocaine has been shown to increase this outward current thereby leading to a slower rate of depolarization during phase 4 and slower impulse initiation in ectopic pacemakers [46]

This lesser sensitivity to lidocaine of atrial as compared to ventricular tissues was studied by Kabela [47] He observed that lidocaine (2 µg per milliliter) induced a greater efflux of K_{42} from canine ventricular muscle and Purkinje fibers pretreated for one hour with the isotope than from atrial muscle He interpreted this result to mean that lidocaine has a greater effect on K^+ conductance in ventricular myocardial fibers and specialized conducting tissues than in the atrium This might explain the relatively greater antiarrhythmic efficacy of the drug in instances of ventricular arrhythmias The basis for these assumed differences in the K^+ conductance of atrial and ventricular tissues remains to be demonstrated

mal saline[58] However a recently reported study of a large group of patients indicates that lido caine does have an antifibrillatory effect in pa tients with acute myocardial infarction[59]

Methyl lidocaine

The antiarrhythmic efficacy of the quaternary derivative of lidocaine methyl lidocaine recently has been investigated by Gillis and associates[60] and by Kniffen and associates[61] Their results suggest possible therapeutic advantages of this agent In experimental animals methyl lidocaine appears to be as effective as lidocaine in abolish ing ventricular arrhythmias resulting from digi talis toxicity or from coronary occlusion No com parable clinical data are available yet The dura tion of action of methyl lidocaine is much longer than that of lidocaine lasting for over 3 hours in some instances (as compared to less than 20 minutes for a single injection of lidocaine) If methyl lidocaine has a comparably long duration of action in man this would obviate the diffi culties which accompany prolonged lidocaine ad ministration In addition methyl lidocaine in plasma concentrations as high as 10 μg per milli liter does not cause the central nervous system toxicity characteristic of lidocaine

This long duration of action and absence of central nervous system toxicity are a result of the quaternization of lidocaine Quaternary com pounds are permanently charged, unlike tertiary amines such as lidocaine which are present in the charged and uncharged forms The charged methyl lidocaine molecule is lipid insoluble and therefore has a smaller volume of distribution than the uncharged lidocaine molecule In addi tion metabolism by the liver is probably slower than that for lidocaine since lipid solubility is im portant for a drug to gain access to the appropri ate liver enzymes

If methyl lidocaine is demonstrated clinically to have the same efficacy duration of effect and lack of toxicity indicated in experimental studies its availability will enhance our abilities to ad minister long term lidocaine therapy to ap propriately selected patients

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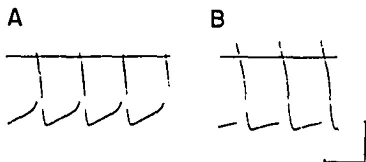


Fig 8 Effect of lidocaine on phase 4 depolarization Blood superfused Purkinje fiber at plasma [K+] = 3 mM Fiber is being stimulated at cycle length of 1 sec In *A* control there is marked phase 4 depolarization In *B* following attainment of a plasma lidocaine concentration of 4 μg per milliliter the slope of phase 4 has decreased, resulting in an increase in activation voltage for the action potential and in action potential amplitude Scale = 40 mV and 1 sec Temp 37°C (Rosen Merker and Pippenger)

and associates[51] reported a patient (with right bundle branch block and left axis deviation) who had a cardiac arrest after lidocaine and Gianelly and associates[52] described two instances of heart block which followed lidocaine administration Finally Gupta Lichstein and Dhadda[26] studied 21 patients with intraventricular conduction abnormalities in two of whom lidocaine induced complete heart block distal to the His bundle These reports all have in common the fact that lidocaine was administered to patients with disease of the A V conducting system They serve to emphasize the fact that despite its relative lack of deleterious effects on the normal heart, lidocaine may seriously impair conduction in the presence of an already diseased conducting system

Recent studies by Giardina and Bigger[53] have indicated that plasma lidocaine concentrations which abolish coupled ventricular premature depolarizations are associated with a decreased Q T interval of the premature impulse as well Giardina[54] has also suggested that lidocaine at times may decrease the QRS duration of premature depolarizations, implying improved conduction for these ectopic impulses This is consistent with the suggestion that in some instances lidocaine may improve conduction in diseased tissues where re entry is occurring (Fig 2 *C*) Such an effect might be expected in instances where phase 4 depolarization is responsible for a loss of membrane potential and slowing of conduction By decreasing the slope of phase 4, lidocaine could increase the activation voltage (Fig 8) and thereby increase action potential amplitude and upstroke velocity, and the conduction velocity of a propagated impulse

A recent study of the actions of lidocaine on ischemic or infarcted myocardium in dogs has shown that it markedly depresses conduction and prolongs the effective refractory period of ventricular muscle in the ischemic zone[55] These differences in the electrophysiologic effects of lidocaine on ischemic and normal tissues have several possible explanations as discussed by Kupersmith, Antman, and Hoffman[55] For example the pH of infarcted tissues is lower than normal and as pH decreases a greater proportion of lidocaine (which has a pKa of 7 86) would be in the ionized form Since ionized lidocaine is the more active form of the drug with respect to local anesthetic effect, the presence of low pH might be expected to enhance its activity[55]

In addition, infarcted tissues have a higher $[K^+]_0$ than normal during periods of cell necrosis Singh and Vaughan Williams[30] have demonstrated that the depressant effects of lidocaine are enhanced as $[K^+]_0$ increases The presence of a high $[K^+]_0$ in an infarcted region might be expected to potentiate the depressant effects of lidocaine on conduction and refractoriness

Studies of the effects of lidocaine on cardiac excitability (defined by the strength of a pulse necessary to excite the heart at different phases during the cardiac cycle) have shown no particular effect in this variable[4] In experiments concerning the ventricular fibrillation threshold in dogs Bacaner[56] reported that lidocaine had little or no effect It is questionable, however whether therapeutic plasma lidocaine concentrations were maintained in his studies More recently Gerstenbluth Spear and Moore[57] restudied this problem and found that therapeutic plasma lidocaine concentrations do significantly increase the ventricular fibrillation threshold.

Clinical studies have provided contradictory results with regard to the efficacy of lidocaine on in situ cardiac arrhythmias Although there is general agreement that the drug is efficacious in the treatment of many ventricular arrhythmias[3] double blind trials have indicated that it is less useful in the therapy of multifocal premature depolarizations or R on T ectopics than it is for unifocal ventricular premature depolarizations[58] There are also reports of equal incidences of ventricular tachycardia and fibrillation in patients receiving lidocaine or equivalent amounts of nor

Annotations

Mexiletine

The management of patients with ventricular arrhythmias remains a difficult problem Although intravenous lidocaine is usually effective in the acute situation particularly after myocardial infarction, 20 to 30 per cent of the patients remain who are resistant even in maximum tolerated doses [1,2] The choice of alternative or concurrent therapy is difficult largely because the second line drugs are either relatively ineffective poorly tolerated, or undesirable for hemodynamic reasons

The prognosis and treatment of patients with chronic ventricular arrhythmias are also subjects of great interest [1 5] Many recent studies in patients with ischemic heart disease have shown a relationship between sudden death and previously noted ventricular arrhythmias [5 7] It is not clear whether this is a direct relationship though this is strongly suggested in some series Although long term reduction of ventricular arrhythmias is demonstrable evidence that any currently available prophylactic agent will, in fact, reduce the incidence of sudden death in these patients is unclear Identification of high risk groups with chronic ventricular arrhythmias and coronary heart disease is however possible and it seems logical to treat these arrhythmias

The commonly used long term oral anti arrhythmic drugs have serious disadvantages Procainamide has an unacceptable dose regime and withdrawals due to the drug reactions or a positive antinuclear antibody are extremely common [8 9] Quinidine is unpopular as a prophylactic agent because of the high frequency of toxic reactions—gastrointestinal disturbances being common while major arrhythmias and even death from ventricular fibrillation have been reported.[10] Diphenylhydantoin though theoretically useful has not proved particularly successful [11] β Adrenergic blocking drugs [12 13] though quite often effective have the disadvantage of depressing cardiac contractility

Mexiletine is a new drug which has recently been found successful in the treatment of ventricular arrhythmias It is a primary amine with certain structural similarities to lidocaine but with very different pharmacokinetic properties It has a long half life and is effective when given orally It was originally found to have anticonvulsant activity in dogs and subsequent studies revealed potent anti arrhythmic properties [14 15]

Preliminary clinical studies in Edinburgh[16] and Belfast[17] involving about 200 patients show that it is at least as effective as other drugs used in the treatment of ventricular arrhythmias In one study [16] only 7 per cent out of 59 patients

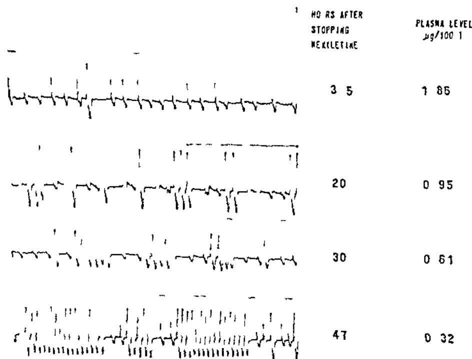


Fig 1 Mexiletine withdrawal in a 63 year-old man with ischemic heart disease and recurrent ventricular tachycardia Serial electrocardiograms and plasma levels, showing increasing ventricular arrhythmias as the plasma level falls.

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Annotations

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The commonly used long term oral anti arrhythmic drugs have serious disadvantages Procainamide has an unaccept able dose regime and withdrawals due to the drug reactions or a positive antinuclear antibody are extremely common [8,9] Quinidine is unpopular as a prophylactic agent because of the high frequency of toxic reactions—gastrointestinal dis turbances being common while major arrhythmias and even death from ventricular fibrillation have been reported.[10] Di phenylhydantoin though theoretically useful has not proved particularly successful [11] β Adrenergic blocking drugs [12,13] though quite often effective have the disadvantage of de pressing cardiac contractility

Mexiletine is a new drug which has recently been found successful in the treatment of ventricular arrhythmias It is a primary amine with certain structural similarities to lido-caine but with very different pharmacokinetic propertie It has a long half life and is effective when given orally It was originally found to have anticonvulsant activity in dogs and subsequent studies revealed potent anti arrhythmic proper ties [14,15]

Preliminary clinical studies in Edinburgh[16] and *Belfast*[17] involving about 200 patients show that it is at least as effec tive as other drugs used in the treatment of ventricular ar rhythmias In one study [16] only 7 per cent out of 59 patients

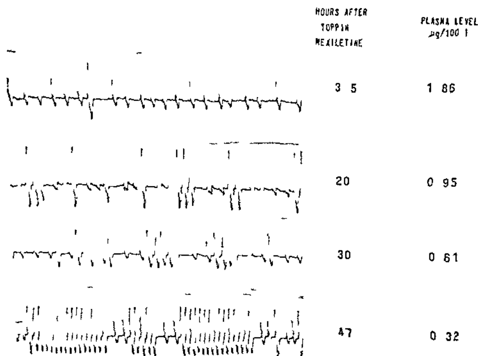


Fig 1 Mexiletine withdrawal in a 63 year-old man with ischemic heart disease and recurrent ventricular tachy cardia Serial electrocardiograms and plasma levels showing increasing ventricular arrhythmias as the plasma level falls

failed to show some response and complete success was seen in 72 per cent Used intravenously it was frequently effective when lidocaine had failed although a relatively high incidence of toxic effects was seen Nausea or vomiting particularly after initial bolus injection occurred in 20 per cent of patients More worrying cardiovascular toxicity (hypotension sometimes associated with bradycardia or supraventricular arrhythmias) was observed in 14 per cent of the patients although most of these were particularly ill with acute myocardial infarction and had received many other anti arrhythmic drugs Its present status as an intravenous agent therefore is probably as additional or alternative therapy in cases otherwise uncontrolled

Oral Mexiletine has given more encouraging results and is effective easy to administer and relatively free from toxic effects In Edinburgh a series of 25 patients with chronic ventricular arrhythmias has now undergone long term therapy for up to eighteen months Suppression of ventricular arrhythmias was checked at frequent outpatient visits and by portable 24 hour electrocardiogram tape recordings In addition efficiency of treatment was assessed by observing the effect of withdrawal of therapy in hospitalized patients with continuous monitoring of the electrocardiogram (Fig 1) These studies were uncontrolled but the effectiveness and absence of clinical hematologic or biochemical evidence of toxicity are very encouraging Furthermore therapeutic plasma concentrations are easily maintained with an eight hour oral dose regimen Currently the drug is being further assessed by long term controlled studies

Although relatively early it appears that Mexiletine is potentially useful—particularly as a long term oral antiarrhythmic—and as such deserves further evaluation

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Tachyarrhythmias and transient cerebral ischemic attacks

It has been extensively documented in the literature that extreme bradycardia and cardiac standstill are commonly associated with signs of generalized cerebral ischemia Several authors also mention that paroxysmal tachyarrhythmias may induce dizziness or syncope but only very few studies have provided objective data to assess the real importance of this problem [1-6] The main reason for this lack of data is that intermittent tachyarrhythmias constitute a real diagnostic challenge [2,3] The routine electrocardiogram is of little help since it is seldom recorded during the acute attack and is

Table I Routine electrocardiogram in 95 patients with dizziness or syncope

Normal electrocardiogram	53
Morphologic abnormalities	
Myocardial infarction	6
Left ventricular hypertrophy	1
Abnormal repolarization	2
Dysrhythmias	
Premature atrial contractions	2
Premature ventricular contractions	6
Controlled atrial fibrillation	2
Sinus bradycardia	1
Conduction disturbances	
Left bundle branch block	4
Left anterior hemiblock	1
Bilateral bundle branch block	3
Atrioventricular block first degree	2
Atrioventricular block, second degree	1
Wolff Parkinson White syndrome	1
Normally functioning pacemaker	13

often normal in between.[5] Continuous monitoring is unappropriate in such cases since it requires hospitalization of otherwise healthy subjects in an intensive-care area where they can only be studied in a resting state With telemetry the heart rhythm can be followed during certain physical activities Its use for detection of paroxysmal tachyarrhythmias is however limited since the receiver has to be in close vicinity to the patient furthermore an observer has to continuously watch the tracing displayed on an oscilloscope to detect major changes in heart rhythm These diagnostic problems and shortcomings are avoided by continuous electrocardiography on a portable tape recorder performed during normal daily activities until the symptoms occur (dynamic electrocardiography) this system also includes a method of accelerated tape analysis as described by Holter[7]

During the past three years, we have used dynamic electrocardiography (DCG) for detection of cardiac dysrhythmias and evaluation of the effectiveness of chronic antidysrhythmic therapy Close to 5 000 tape recordings have been performed on 587 patients In 95 cases DCG was performed because the patients had shown unexplained dizziness (55 patients) or syncope (40 patients) In all patients the clinical neurologic and cardiac examination was normal the routine electrocardiogram could not provide an explanation for the symptoms in any of the patients (Table I) The age of the patients ranged from 16 to 81 years (mean 57 8 years)

The patients were classified into four categories according to the results of the tape analysis (Table II) In 22 patients (23 1 per cent) no electrocardiographic abnormalities could be detected on repeated DCG recordings (Group I) in 46 patients (48 4 per cent) the findings definitely correlated with the occurrence of dizziness or syncope (Group II) findings possibly related to the symptoms were identified in 42 patients (Group III) and 17 patients showed abnormalities of the heart rhythm or conduction not related to the symptoms (Group IV) Similar results have been found by Stern and coworkers[4] in a series of 44 patients with complaints of transient cerebral ischemic attacks

Table II DCG findings in 95 patients with dizziness or syncope*

I	*No abnormalities detected*		22
II	*Findings definitely correlating with symptoms*		46
	Paroxysmal atrial fibrillation	6	
	Paroxysmal atrial flutter	1	
	Paroxysmal atrial tachycardia	11	
	Ventricular tachycardia	10	
	Sinus bradycardia	3	
	Sino atrial block or standstill	5	
	Atrio-ventricular block second degree	4	
	Atrioventricular block third degree	3	
	Defective pacemaker	5	
III	*Findings possibly related to symptoms*		42
	Frequent premature atrial contractions	11†	
	Frequent premature ventricular contractions	31‡	
IV	*Findings not related to symptoms*		17
	Sinus tachycardia (≥120 bpm)	8	
	Sinus bradycardia (≤50 bpm)	1	
	Intermittent bundle branch block	3	
	Atrioventricular block, first degree	5	

Whenever a pati nt presented different types of arrhythmia or conduction d fect, he was always listed under each separate item.
†F e patients devel ped paroxysmal atrial tachycardia two patients dev loped atri l fibrill tion
‡Ten patients developed ventricular tachycardia

In the majority of patients in Group II the symptoms were due to supraventricular tachyarrhythmias (18 cases) The onset was always sudden in 7 patients the acute attack was preceded by frequent premature atrial contractions The rate of the tachycardia varied from 135 to 218 beats per minute (bpm) showing that relatively low heart rates may have serious hemodynamic consequences A tachycardia occurring in a normal subject is usually asymptomatic as long as the heart rate remains below 160 bpm higher heart rates produce a sharp drop in cardiac output[9 11] Symptoms may however appear at lower heart rates A drop in cardiac output may indeed be precipitated by the presence of heart disease[6] Symptoms of focal or diffuse cerebrovascular ischemia can also be potentiated by unsuspected or asymptomatic underlying cerebrovascular disease[2 4 8] This factor certainly accounts for the symptoms in certain patients of Group II in whom the rate and type of the dysrhythmia would not be expected to produce dizziness or syncope The age of the patients also favors this hypothesis 25 patients were 65 years old or more (range 19 to 81 years mean 61 4 years)

In 10 patients the symptoms were due to ventricular tachycardia The earlier DCG tracings had shown premature ventricular contractions (PVC) at some time in all of these patients The PVC s were continuous in three patients intermittent (more than 50 per cent of the recording) in three patients, and episodic (less than 50 per cent of the recording) in four patients they were frequent (more than 5 per minute) in six patients multifocal in five patients and repetitive in four

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of children whose elevation was observed at the age of 5 years At the age of 11 to 12 years these children had significantly higher blood pressures than their matched controls[2] The mean difference between the paired children was only 9 for systolic pressure and 6 for diastolic Such differences however represent 10 per cent of the average level of blood pressure at ages 11 to 12 If a 10 per cent increase persisted they would have *on the average* a blood pressure of 141/88 when they reached the age of 35 to 44 years a level which corresponds to the 80th percentile This extrapolation is based on the figures for U S Caucasian males given by Acheson[3]

A leading article in the *British Medical Journal* has recently commented on my study and on the whole issue of detecting and treating juvenile hypertension[4] The article quite properly cautions against premature attempts to treat asymptomatic children with drugs whose long term toxicity we do not know and whose effects upon children might be qualitatively different from their effects upon adults Having made this important point the leading article goes on in a vein of somewhat irrational pessimism that I cannot entirely follow

The expense inconvenience and possible psychological harm of screening children for hypertension is mentioned It seems to me that these difficulties would be no greater for children than for adults in fact the inconvenience would probably be less. If we had an effective safe treatment its benefits in preventing death or disability would have to be weighed against the problems of screening no matter what the target age group was If the benefits were greater with treatment started in childhood and the screening difficulties no greater a net gain would be achieved

The article suggests as a possible compromise that continued surveillance of blood pressure might be restricted to children with a strong parental history of high blood pressure One difficulty here would be in the detection of hypertension in the parents There is a more important objection however Unless the hypertensive child of hypertensive parents is more likely to show progression than the hypertensive child of normotensive parents such a policy would not specifically select for treatment the children at highest risk Londe and colleagues[1] found that half the children with elevated blood pressure had hypertensive parents but he offered no evidence that the *persistence* of childhood hypertension was dependent on the family history One must recognize that although blood pressure has strong hereditary determinants once the pressure is elevated the prognosis may not be influenced appreciably by genetic factors If it is not parental history would be worth taking into account only if limited facilities obliged one to aim the initial screening program at a target group with the greatest potential yield of positives

My opinion is that we should press on with large scale studies of the significance of elevated blood pressure in young children in order to be ready to take advantage of any therapeutic innovation that could safely be used in childhood.

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Diffuse training programs

There is a trend in the education of a specialist in cardiology to impose upon the trainee brief experiences and courses in many branches of medical and even non medical sciences It is considered good practice for him to spend about three months each in the fields of mathematics electronics physiology statistics, epidemiology biochemistry pathology cardiac catheterization and hemodynamic physiology electrophysiology and even in languages, humanities and computer programing He is also expected to do serious fundamental research and even prepare for his board examinations in clinical internal medicine and the subspecialty of clinical cardiology This type of multiphasic training appears impressive when listed on a curriculum vitae form on training The non critical reader would immediately consider him an extremely well trained scientist with great promise who is prepared for any development in the near and distant future

But, what about his performance and his capabilities? Can he design an amplifier develop a mathematical solution for rates of exchanges and physiochemical reactions in multiple compartments, solve problems in rheology understand an enzymatic reaction and energy exchange involving thermodynamic principles speak another language or dare unaided, to write and sign a contract in another language? No he could not do these things He would be as well trained in these various fields of science as would a language student be in any one language who matriculates in a language department after spending three months each studying French, Spanish Greek, Latin, Sanskrit, heiroglyphics German, Russian and Chinese Such a language student might remember the alphabet or a few symbols, but he would not be well trained in a single language and probably not even in his native one

Therefore what is the objective in training in cardiologic research? It is to produce investigators who can think creatively perform well organized and well directed research

patients The R on T phenomenon was present in four cases This emphasizes the premonitory value of certain types of PVC s for the subsequent development of ventricular tachycardia It should be noted however that the continuous electrocardiogram recorded during the hour preceding the tachycardia did not show any PVC s in three patients

In 42 patients (Group III) frequent premature atrial and ventricular contractions were discovered by DCG 17 of the patients subsequently developed an acute tachyarrhythmia The rate of positive findings in these patients is influenced on one hand by the frequency of their transient ischemic attacks and on the other hand by the duration of DCG recording A positive conclusion (whether or not the symptoms are due to a cardiac dysrhythmia or a conduction defect) can only be drawn when the symptoms occur during the continuous recording The mean recording time for the patients with positive findings was 68 hours The prevalence of tachyarrhythmias in the whole group would probably have been higher if the recording had been extended in some patients. For practical reasons however we have limited the recording time to one week

It has been stated repeatedly that the routine electrocardiogram recorded between attacks is abnormal in most cases[2,6] As can be seen from Table II this was not the case in the present study In 53 patients (55 8 per cent) the electrocardiogram was normal in nine patients it showed morphologic changes not related to the clinical symptoms In 23 patients (24 2 per cent) mild dysrhythmias or conduction defects were present although none of these abnormalities could explain the appearance of generalized cerebral ischemia one could suspect that an increase in the number of ectopic beats or worsening of the atrioventricular conduction might induce dizziness or syncope Such electrocardiographic abnormalities are however also frequently encountered in asymptomatic patients and are therefore meaningless as such

All patients in Group II received antidysrhythmic treatment sometimes combined with cardiac pacing Relief of the symptoms was complete in 33 patients (71 7 per cent) partial relief was obtained in eight patients (17 4 per cent) in five patients (10 8 per cent) the symptoms remained unchanged Our results confirm in a larger group those published sporadically by previous authors[1 2 4 6]

These data suggest that a complete cardiac examination should be performed in all patients with unexplained transient cerebral ischemic attacks If no cardiac abnormalities are discovered the patients should be submitted to continuous electrocardiographic recording until the symptoms occur

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The detection of essential hypertension in childhood

The early detection and treatment of essential hypertension are very important issues in preventive and clinical medicine today Unfortunately we do not yet have an effective hypotensive drug free of immediate side effects and without danger from long term use Given the current interest in the problem it is likely that an acceptable method of treatment will be developed That physiological methods might supplant the pharmacological attack upon hypertension is a possibility suggested by conditioning experiments in the self control of blood pressure

Meanwhile it is important to determine the earliest age at which hypertension can be detected given the likelihood that the sooner a safe form of treatment were started the better would be the protection against progression of the disease This point would not be invalidated by the discovery that essential hypertension is not one disease but several

Londe and his colleagues[1] have shown that elevated blood pressure in children tends to persist After Londe s follow up of children who were under age 15 when they were first found to have elevated blood pressure I carried out a small study

Partial cardiopulmonary bypass and pulmonary embolectomy

To the Editor

The editorial by Drs. Beall and Collins raises a very significant point. They state that the technique of partial cardiopulmonary bypass is available to support critically ill patients until pulmonary angiography can be done, while it is being performed, after it is performed, and until preparations can be made for pulmonary embolectomy—if it is indicated. Dr Beall's extensive experience with this technique indicates that it is a feasible method of supporting such patients.

The critical issue is how often this procedure is needed, how it would affect the number of patients who might profit from pulmonary embolectomy, and, most important, how its use would affect the mortality of acute pulmonary embolism.

We note that Drs Beall and Collins agree that pulmonary embolectomy can be performed only from among certain patients in whom the diagnosis of acute pulmonary embolism is established by pulmonary angiography. The critical prelude to the performance of pulmonary angiography is suspicion of the diagnosis of acute pulmonary embolism. Therefore one must determine the following: Do patients die of pulmonary embolism because their physicians have not been sufficiently well *organized to institute* partial cardiopulmonary bypass, or do the 200 000 people who die of pulmonary embolism each year in the U S[1] die because the diagnosis has not been suspected. The evidence is overwhelming that it is the latter.

If one reanalyzes our data to see what impact the immediate availability of partial cardiopulmonary bypass might have had during this ten year period, we find the following. First, how many patients *who were suspected of having pulmonary embolism* died before pulmonary angiography could be performed? Drs Beall and Collins state that *in the ten* year period from 1964 to 1974, 310 patients died of pulmonary embolism at our hospital. Analysis of these data will be needed to determine how many patients actually had pulmonary embolism, in how many it was the primary cause of death, and most important, in how many cases was the diagnosis suspected prior to death.

The second question is: How many patients died during pulmonary angiography? The answer to this question is two patients. Therefore one can question, would the availability of cardiopulmonary bypass have prevented these two deaths? One of the deaths was a patient with terminal primary pulmonary hypertension. Pulmonary embolectomy clearly would not have been beneficial to this patient. A *second patient* with massive pulmonary embolism with obstruction of 75 per cent of the pulmonary vasculature suffered a cardiac *arrest at the time* of pulmonary angiography. She was resuscitated and had multiple cardiac arrests until she died 60 minutes after the *procedure. The fa t that* she was 77 years old and had adenocarcinoma of the rectum indicated in our judgement that pulmonary embolectomy *was not clinically* appropriate.

The next group to look at is patients with massive embolism documented by pulmonary angiography who died before pulmonary embolectomy could be performed. We had one such patient who died 30 minutes after the diagnosis of acute pulmonary embolism had been *documented* by pulmonary angiography. We agree that if partial cardiopulmonary bypass had been immediately available she might have survived. She was a 69 year-old woman who had severe chronic obstructive pulmonary disease with cor pulmonale prior to the episode of acute pulmonary embolism. The appropriateness of pulmonary embolectomy in her case remains a moot point.

Thus if we had had cardiopulmonary bypass immediately available during this ten year period of time, it is possible that *one* of the deaths due to documented pulmonary embolism might have been prevented by pulmonary embolectomy!

We do not mean to belittle the role of partial cardiopulmonary bypass. Our point is that the availability of cardiopulmonary bypass at our hospital would not have had a significant impact on the mortality of acute pulmonary embolism during the ten year period under study. We believe that most deaths due to acute pulmonary embolism occur *because* the diagnosis is not suspected and treatment is not instituted.

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Propranolol in orthostatic tachycardia

To the Editor

In the paper "Propranolol in the treatment of orthostatic tachycardia associated with orthostatic hypotension," in the October 1974 issue of THE JOURNAL (88 493, 1974) the authors suggest that the *efficacy of propranolol* was due to its prevention of excessively rapid heart rates. This allowed *maintenance* of a relatively normal cardiac output, and thereby arterial pressure was more easily controlled. Perhaps it may be argued that the control of the *arterial* blood pressure was not a consequence of control of the tachycardia.

Wiggers[1] noted that cardiac output fell only when the heart rate exceeded 180 beats *per minute*. Wolff[2] concurred, reporting that, clinically, 50 per cent of normals, as well as people with coronary artery *disease*, experienced vascular collapse at 180 beats per minute. Weissler and colleagues[3] studying atropine induced *tachycardia* found that with a rate change from 80 to 140 beats per minute, cardiac output increased. Since the authors' *patient* did not have a rate above 140 beats per minute, it *is not clear* that her tachycardia caused a fall in cardiac output.

An alternate explanation for the results obtained by the authors is available. *Blockade of the* beta adrenergic receptors not only slows the heart *rate*, it also prevents beta adrenergic dilatation of peripheral vessels. This causes an increase in peripheral resistance and a tendency toward elevation of the blood *pressure*.[4] *This* principle is illustrated by the observation that the administration of propranolol increases

into new ideas and concepts, understand and interpret intelligently and carefully their data, and ultimately present new information and concepts to the field of cardiology The trainee or student who undertakes a multidisciplinary training course would not be an independent thinker or investigator could not design a good experiment, would not have an original thought or do creative thinking He may be a fair technician and at best may do pedestrian research, collect data and draw curves or repeat studies of others with new apparatus or material His research would be poor his objectives not of the highest order and his mind and thinking in a rut Such training may be acceptable for a technologist, administrator expert in grantsmanship or empire builder and committeeman.

It seems that such multidisciplinary research programs are begging for students judging from the announcements letters, pamphlets placards and other advertisements received in the daily mail from various laboratories Such recruitment offering good salaries will induce inadequate trainees who would ultimately clutter the literature with more of the same information

There is a need to realize the immense value and tremendous privilege associated with working with a master in any field of human endeavor including science By all means do not overburden the master with trainees programs and principles dictated by committees or by those less able Fortunately there are a few who realize the importance of this and who support such policies so that masters are not overburdened. There is no greater experience than working and training with a master especially one who can think creatively clearly logically and deliberately Some of the greatest students trained under great men and in an isolated field. Most masters of the present trained under masters of the past. The masters were able to project their genius into the future by training others in the disciplines and methods of research Unfortunately outstanding students and trainees are rare and difficult to locate A most satisfactory criterion of such a student is the master s willingness to accept him for several years. The great need in science is creative thinkers and investigators who really know research discipline and values. Surely technologists and investigators for pedestrian research must be kept in supply but never at the expense of creative thinkers who produce considerable amounts of original work. There is a need to study and influence favorably training programs in medical research, including cardiology to provide outstanding investigators for the future who may be responsible for an important discovery

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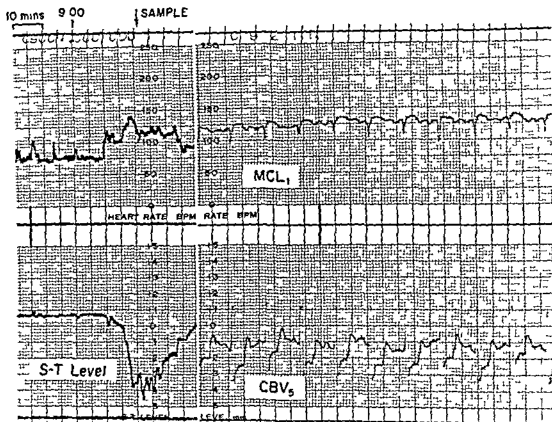


Fig 1 Left and Right Two channel Holter recordings *Left*, trend analysis print-out indicates at approximately 9 21 P.M. a heart rate (top) of 130 beats per minute and S T level (bottom) depression of 3 to 4 mm *Right* real time sample print-out at 9 21 P.M. confirms 3 to 4 mm of ischemic ST segment depression in chest bipolar V_5 (CBV_5) lead.

Silent clinical symptoms associated with ST segment depression [1] angina pectoris [2] or ischemic heart disease[3] have received recent attention in the literature Our observations[4] are similar to that reported by Dr Burch in identifying dyspnea without precordial or anginal symptoms as being present in patients with concurrent ischemic ST segment depression which is relieved by rest or sublingual nitroglycerin Clinicians should be aware of this finding in the management of patients diagnosed or suspected of ischemic heart disease

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4 Kennedy H L Underhill S J Caralis D and Warbasse J R Ischemic ST segment depression without precordial or anginal symptoms detected by Holter recordings (To be submitted)

Accelerated AV conduction and complete A V block

To the Editor

The article entitled "Accelerated A V conduction associated with complete A V block by Drs Krishnaswami and Geraci (AM HEART J 88 463 1974) is interesting However the term accelerated A V conduction is a misnomer Perhaps the authors meant accelerated A H conduction But even if this was so an A H interval of 80 msec does not represent faster than normal conduction velocity The most that can be said is that the A H interval was at the lower limits of normal What they did find was that the A H did not increase during atrial pacing at increasing rates up to 130/min This is probably significant although it would have been interesting to see at what rate A H Wenckebach developed

the rise in blood pressure following norepinephrine[5] Propranolol apparently not only prevents beta arteriolar dilatation but also displaces norepinephrine from beta receptors so that it becomes more concentrated at the alpha sites which cause arteriolar constriction

Although propranolol is commonly used in the treatment of hypertension where it is thought to be helpful by lowering cardiac output it increases the blood pressure under certain circumstances. It may precipitate a hypertensive crisis with pheochromocytoma[6] by permitting unopposed alpha stimulation In a diabetic it caused hypoglycemia with a secondary adrenergic response and extreme hypertension[7] because alpha stimulation was not balanced by beta stimulation. A similar mechanism has been invoked to explain complete heart block (by vagal reflex) occurring when propranolol and epinephrine were given at the same time[8] In addition, peripheral arterial insufficiency has been observed in patients taking propranolol[9] giving further evidence of peripheral constriction

Finally we wish to call attention to the decrease in sodium excretion which has been found with the use of propranolol[10] This would tend to increase the blood volume and minimize the effect of peripheral vascular pooling as a factor in orthostatic hypotension

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Reply

To the Editor

Doctors Barch and Lawrence have appropriately focused an important pharmacologic action of propranolol which may well have played a therapeutic role in the patient we reported. Indeed, I plead particular sin for our not having discussed this possibility inasmuch as Doctors Luria Kaplan, and I actually treated prolonged hypotension with a beta receptor blocking agent in 1964[1] We did discuss peripheral vasoconstrictor properties of beta blockers in that paper and mentioned the possibility that neurotransmitter substance was displaced from beta to alpha sites in the periphery

In our recent paper we perhaps did overly emphasize relief of the orthostatic tachycardia as the explanation for the patient's subjective improvement While I gladly accept the appropriate chastisement from Doctors Barch and Lawrence I would like to again emphasize our major message Namely propranolol did effectively slow orthostatic tachycardia without adverse side effects

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Ischemic ST segment depression and dyspnea

To the Editor

The annotation entitled Silent angina and coronary bypass surgery" by Dr Burch in the October 1974 issue of the JOURNAL (88 530 1974) emphasizes the absence of angina pectoris and chest discomfort and the presence of dyspnea associated with ST segment depression after a Master two-step test This dyspnea manifested upon stress was quickly relieved by rest and sublingual nitroglycerin Our experience with ambulatory 24 hour Holter recordings confirms the observation that ischemic ST segment depression may present with the clinical symptom of dyspnea only

An illustrative case J M J a 57 year old active male presented completely asymptomatic as a normal participant in a two channel 24 hour Holter recording protocol Trend analysis revealed seven episodes of ischemic ST segment depression encompassing a total time of 210 minutes the most striking of which (Fig 1) was precipitated by a brisk walk Patient diary revealed no symptoms and query of the patient within one hour of completion of the Holter recording elicited in retrospect, only the presence of mild dyspnea during the brisk walk Treadmill testing utilizing the Bruce protocol was performed for 370 seconds reaching a maximal blood pressure of 154/80 mm Hg and a maximal heart rate of 170 beats per minute with 4 5 mm of ischemic ST segment depression before being terminated with exertional hypotension accompanied by dyspnea The patient denied angina pectoris or chest discomfort Angiography revealed a 70 to 80 per cent narrowing of the left main coronary artery 80 to 90 per cent narrowing of the proximal left anterior descending coronary artery and a normal left ventricular ejection fraction of 58 per cent Left ventricular end diastolic pressure was normal and calcification was noted in the left main and proximal left anterior descending coronary arteries

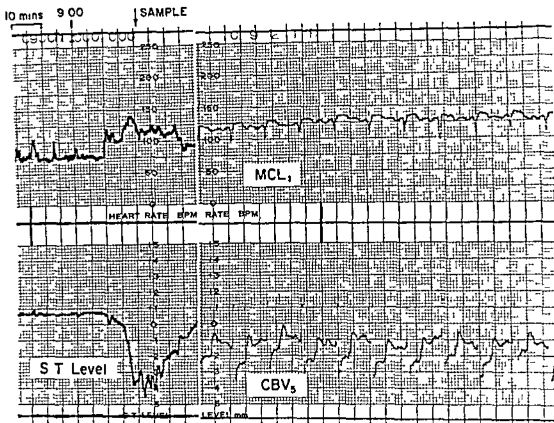


Fig 1 Left and Right Two channel Holter recordings *Left* trend analysis print out indicates at approximately 9 21 P.M. a heart rate (top) of 130 beats per minute and S T level (bottom) depression of 3 to 4 mm *Right* real time sample print-out at 9 21 P.M. confirms 3 to 4 mm of ischemic ST segment depression in chest bipolar V_5 (CBV_5) lead.

Silent clinical symptoms associated with ST segment depression,[1] angina pectoris [2] or ischemic heart disease[3] have received recent attention in the literature Our observations[4] are similar to that reported by Dr Burch in identifying dyspnea without precordial or anginal symptoms as being present in patients with concurrent ischemic ST segment depression which is relieved by rest or sublingual nitroglycerin Clinicians should be aware of this finding in the management of patients diagnosed or suspected of ischemic heart disease

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Accelerated AV conduction and complete A V block

To the Editor

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Drs Krishnaswami and Geraci were probably dealing with an elusive type of ventricular pre excitation usually ascribed to a total (but in this case probably partial) *A V nodal bypass* This entity is not characterized by the length of the P R or A H intervals or QRS duration The common denominators are from the clinical viewpoint the history of repetitive supra ventricular tachyarrhythmias and for the electrophysiologi cal side the abnormal response to pacing as qualified by the authors

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Reply

To the Editor

Dr Castellanos comment that the title of the article Ac celerated A V conduction is a misnomer is quite correct We had the problem of choosing a title to describe a condition that was deciphered during a routine electrophysiological study Perhaps Accessory A V nodal pathway associated with complete A V block is the best title for this article for that is what actually exists

We admit that A H1 is not truly accelerated but we chose the title for its ability to draw attention to the unusual coex istence of two conditions Had we not atrially paced this pa tient and obtained a lack of A H1 prolongation we would have never been able to surmise the possibility of accessory pathway and so would have never explained her previous episodes of supraventricular tachycardia

Dr Castellanos is perfectly correct in his comment. We were indeed dealing with an elusive type of ventricular pre excitation of the James fiber type with normal P R (before the development of block) and normal A H1 with Type III response to atrial pacing No attempt was made to determine at what rate (of atrial pacing) the accessory pathway would show Wenckebach phenomenon We did not feel it would add any relevant data to that already obtained

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Mechanisms of heart sounds

To the Editor

I read with interest the report of Luisada and associates[1] regarding the mechanisms of the heart sounds The authors deemphasize the importance of the mitral valve in the pro duction of the first heart sound Although I do not belong to the group of cardiologists contending that mitral valve ten sion or closure is the only cause of the first heart sound. I think that the mitral valve plays a very important role in the genesis of S_1

I would like to present a tracing showing data conflicting with the theory of Luisada and colleagues, especially the following two points

1 The authors state that the amplitude of the systolic wave of the first derivative of the left ventricular pressure (dP/dt) varies similarly with the amplitude of the first heart sound under a variety of conditions Fig 1 is representative of tracings recorded during left ventricular catheterization in a patient with coronary atherosclerosis and frequent pre

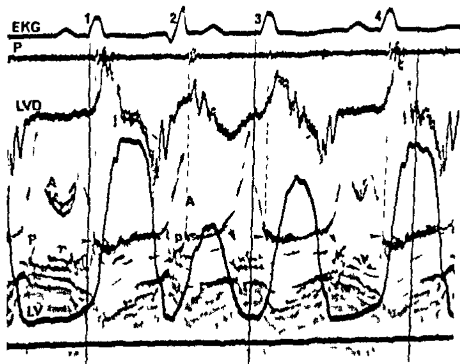


Fig 1 EKG Electrocardiogram P Phonocardiogram LVD First derivative of left ventricular pressure LV Left ventricular pressure A Anterior mitral leaflet P p Posterior mitral leaflet

mature ventricular contractions The amplitude of the first heart sound of beat 2 is higher than the amplitude of S_1 of beats 1 or 3 although the left ventricular dP/dt is lower in beat 2 On the other hand the amplitude of the first heart sound correlates well with the rate of closure of the mitral valve Analysis of 30 beats shows a better correlation of the amplitude of the first heart sound with the rate of mitral valve closure than with the magnitude of left ventricular dP/dt. The increased intensity of the first heart sound in the premature beat (beat 2 in Fig 1) cannot be accounted for by smaller heart size[2] since correlation to previous cycle length or ventricular filling time (open mitral valve by echocardiography) does not explain the observed changes in amplitude of S_1 in this patient

2 The authors state that mitral valve closure precedes the first high frequency component of the first heart sound by 20 to 25 msec In Fig 9 presented by them[1] it is hard to prove that the mitral valve is closed at point B of the echocardiogram since the posterior leaflet was not recorded. In recordings obtained in our laboratory the first high frequency component of the first heart sound coincides with the closure of the mitral valve as demonstrated by apposition of the echoes of the anterior and posterior mitral leaflets (arrows in Fig 1) Similar results were obtained by Burggraf and Craige[3] Laniado and associates[4] utilizing cinefluoroscopy also demonstrated that the first heart sound was simultaneous with mitral closure and followed the crossing point of atrial and ventricular pressures.[4]

Thus it appears that crossing of the atrial and ventricular pressures initiates the mitral closing movement related to ventricular contraction Closure of the valve occurs some msec later because of the kinetic energy (inertia) of the blood flowing in the ventricle The final velocity (and momentum) of the mitral valve and the accompanying blood columns at the moment of closure would depend primarily on two factors. First left ventricular dP/dt (higher dP/dt such as in sympathetic stimulation would cause more acceleration and louder S_1) and second the position of the mitral valve at the onset of ventricular systole (wide open valve such as in short PR or in the premature beat 2 in Fig 1 allows more time for acceleration, thus higher final velocity momentum and amplitude of S_1) At the time of mitral closure sudden deceleration causes the mitral apparatus, the blood, and probably the myocardium to vibrate Part of these vibrations is perceived as sound.

In summary although left ventricular contraction provides the energy needed for the production of the first heart sound, the mitral valve is essential in the transduction of this energy into sound.

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Reply

To the Editor

We owe to echocardiography the knowledge that both valve openings and valve closures are events that require a certain time Most statements of the past mentioning valve closure should be amended to say completion of valve closure

Data found in cases with either *pathological* valves (mitral stenosis) or *pathological* rhythms (A V block) *cannot be used* as such for the interpretation of the events of the *normal* heart. These clinical cases can supply interesting information, which should be evaluated and explained on the basis of the existing abnormality

In spite of the great interest of the data supplied by echocardiography this cannot be considered an exact method of study on account of the variables introduced by the angle of the beam in regard to the plan of a leaflet plus the changing position of the latter induced by motion of the heart on account of both its dynamics and the shift induced by respiration. This explains why coaptation of the mitral leaflets is often seen only every 2 or 3 beats Therefore it should be kept in mind that recording of the motions of the two diverging and converging leaflets by a single beam may lead to inaccuracies. Moreover the tracings of the posterior leaflet are often of poor quality and are interrupted by gaps, at least in subjects without thickening of the leaflets

Full development of the left ventricular pressure rise requires a closed chamber Whenever the mitral valve *is open* at the beginning of LV contraction because of either high LA pressure or abnormal PR length there is an early slow rise of pressure (until the mitral valve closes) and *then an abrupt rise* increased by the fact that by that time the entire left ventricular musculature is contracting

In the document presented by Dr Kostis the second beat is *probably* an upper nodal ectopic beat not only is the atrial contraction abnormal but also *the IV conduction* is altered to the point that the pattern of LBBB usually present disappears. Could this change result in a more efficient *contraction*? We do not know but this question should be raised.

We agree that sometimes the relationship between dp/dt and amplitude of first heart *sound is* not close in certain pathological conditions This had been previously found by Sakamoto and colleagues[1] *in our* laboratory in regard to experimental atrial fibrillation Other factors must be involved. A tremendous increase *in velocity* would be required to overcome the drop caused by *lower pressure* Moreover there is no doubt that a change in ventricular size may cause a different vibrational amplitude

In order to evaluate the interval between completion of mitral valve *closure* and beginning of the first heart sound, one would require a sound tracing of greater amplitude and better *detail*. The particular case that is presented (LBBB) may not have been suitable *for such a* purpose Tracings published by others often show a certain *interval* Another

possibility that is seldom considered is a shift of the vibrations of the first sound to a different frequency band. This could be demonstrated by either spectral analysis or simultaneous recordings with at least two filters (medium and high frequency bands)

Whatever the combination of existing factors the left ventricle is still the power source the LV walls chordae blood, and valves are the vibrating structures If the abnormal closure of the mitral valve has created an abnormal *dynamic situation the vibrations may be altered*

A sound is the result of mass amplitude and time Based on this relationship MacCanon and co workers[2] found a participation of the mitral valve of about 10 per cent to the sound energy of the *normal* first sound Therefore it is obvious that even a marked increase of amplitude and a decrease of time of closure would not be able to account for *the tremendous variations of the first heart sound in* AV block One of the most significant echocardiographic studies in AV block (Shah and associates[3]) explains the changes of the first sound in a satisfactory fashion when the valve is closed before the onset of systole the early rise of LV pressure results in a force of acceleration of small magnitude (small vibrations within LV) the later the valve closes with *respect to the rate of LV pressure rise the greater* are the forces generated (large vibrations within LV) should the valve be kept open by a high LA pressure (mitral stenosis short P R interval) then a prominent first sound would occur Thus timing of valve closure in relation to LV systole may be an important determinant of first sound amplitude even though the source of energy for the vibrations is still derived from LV pressure rise

All our comments do *not* consider the older concept according to which a slapping of the leaflets would cause the first sound. This concept applied to paper thin structures moving in a milieu that has a nearly identical specific gravity would be refused by any physicist Rather they apply to the problem of *tension* of the closed mitral valve (normal heart) and to the *alterations of dynamics* caused by an AV block.

We wish to thank Dr Kostis for his interest. On rereading his letter it becomes obvious that we are not as far apart as it would seem from a cursory glance

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Book reviews

Dye Curves The Theory and Practice of Indicator Dilution Edited by Dennis A Bloomfield London 1974 University Park Press 450 pages $27 50

This monograph thoroughly reviews the significant phases of the development and use of the dye dilution curve in the study of the heart and circulation The seventeen chapters include discussions of history theory methods and technic equipment analysis of curves and applications in clinical practice and research The many contributors are experts in the field of catheterization of the heart They have assisted in developing and applying the methods to clinical medicine The beginner in the cardiac catheterization laboratory will find this book to be of considerable value The mathematical and theoretic discussions are good and well presented so that the analysis of the dye dilution curves can be meaningful to those who learn the theory The chapters include well selected bibliographies This is a good book which should be available in all catheterization laboratories

Vascular Disorders of the Extremities second edition By David I Abramson M D F A C P New York 1974 Harper & Row 898 pages

Diseases of the vascular system of the extremities are exceedingly common and important problems in clinical medicine Yet during the recent period there has been relatively little interest in vascular disease of the limbs. This second edition by Abramson is not only a fine book but a timely one The first edition was received successfully and this edition will be even more valuable Abramson is not only an able clinician but he had contributed extensively to the understanding of vascular physiology and disorders His book reviews the problems extremely well and primarily from the clinical aspects of the diseases Simple procedures and tests of vascular function and disease are described so that a physician can arrive at an accurate diagnosis and estimate of vascular function without the use of complex equipment and investigative procedures At the same time the more sophisticated procedures which are available for use when necessary are discussed. As would be expected, the common disorders of the arterial venous and lymphatic systems are described. Functional arterial as well as organic disorders are nicely presented This is a highly recommended book for a thorough presentation of vascular disorders of the extremities.

Basic Pediatric Electrocardiography By Arno R Hohn M D New York 1974 Medcom Press 271 pages

This book on electrocardiography reviews the basic changes with disease and normal features of tracings in infants and children The presentation is for beginners The text is clear and simple and closely correlated with well selected illustrations The publication is now one of many on electrocardiography but there are so few directed to electrocardiography in pediatrics Therefore students, house staff and all pediatricians will find this to be an interesting and valuable compendium on the interpretation of the electrocardiogram in infants and children.

Complex Electrocardiography 2 Albert N Brest M D Editor in Chief Philadelphia 1974 F.A. Davis Company 317 pages

With the increase in monitoring of patients with heart disease complex electrocardiographic patterns are encountered. This is particularly true in coronary care units where patients with advanced cardiac disease and digitalis intoxication and electrolyte imbalance exist simultaneously This volume of *Cardiovascular Clinics* contains important contributions which should interest all physicians who treat heart disease The disturbances in cardiac rhythms discussed are common and important in the practice of cardiology The contributors are well known They presented their ideas clearly This is an excellent volume and is highly recommended.

Books received

Alexis Carrel—Visionary Surgeon By W Sterling Edwards, M D and Peter D Edwards Springfield Ill 1974 Charles C Thomas Publisher 123 pages Price $5 00

Digitalis *New England Journal of Medicine Medical Progress Series* By Thomas Woodward Smith M D Boston 1974 Little Brown & Company 83 pages Price $8 95

Cardiovascular Surgery 1973 American Heart Association Monongraph No 42 Edited by John Hines Kennedy M D New York 1974 The American Heart Association Inc 276 pages Price $5 00

Surgical Diseases of the Chest 3rd edition Edited by Brian Blades, M D St. Louis 1974 The C V Mosby Company 768 pages. Price $42 50

Cardiac Hypertrophy and Cardiomyopathy *American Heart* Association Monograph No 43 Edited by Jules Cohen, M.D and Pravin M Shah M D., New York, 1974 The American Heart Association Inc 223 pages Price $5 00

Announcements

Symposium on the mitral valve

An international symposium on the mitral valve its physiology blood flowmetry ultrasonic diagnosis and surgery will be conducted on May 26 through May 28 1975 at the Hotel PLM Saint Jacques Paris France The symposium is sponsored by the French Cardiac Society For further information please write Dr D Kalmanson Program Director Department of Cardiology Fondation A de Rothschild 29 rue Manin 75019 Paris, France

American Heart Journal

May 1975 Volume 89 Number 5

Editorial

Ventricular tachycardia

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It seems unfortunate that ventricular tachycardia (VT) a manifestation of a serious and often fatal disorder of the electrical properties of the heart should be so difficult, if not impossible to diagnose from the surface electrocardiogram (ECG) The classical ECG criteria of VT namely A V dissociation and a rapid ventricular rate with bizarre QRS complexes although statistically strongly supporting a diagnosis of VT can also be recorded during episodes of A V junctional tachycardias with either pre existing bundle branch block or aberrancy secondary to a number of different electrophysiologic mechanisms Similarly VT with retrograde conduction cannot be differentiated from an arrhythmia originating in the A V junction The most useful of the ECG criteria of VT—namely captures and fusions—are recorded only rarely in VT and thus their absence is of no aid in the differential diagnosis of VT When feasible the His bundle electrogram or ventricular capture with a more narrow QRS during atrial pacing can as a rule settle this diagnostic dilemma However access to these procedures is limited and the vast majority of physicians have to rely on the surface ECG

In many instances the diagnosis of VT can be made with assurance on the basis of the clinical findings Thus the patient with a tachycardia who is seriously compromized hemodynamically with a heart rate generally between 150 and 180 with either hypotension syncope or dyspnea or any combination of the above and whose cardiac examination reveals a first heart sound of variable intensity a changing systolic blood pressure or pulse pressure and cannon a waves in the jugular pulse most likely has ventricular tachycardia and may require immediate intervention A patient with the same heart rate and electrocardiogram but who is asymptomatic with a first heart sound of constant intensity and no abnormalities in the jugular pulse is more likely to have a supraventricular rhythm although a rare instance of VT with 1 1 retrograde conduction cannot be ruled out with certainty In fact the heart rate and rhythmicity and the hemodynamic state of the patient all determined by the physical examination may at times prove more helpful than the ECG both in establishing the nature of the tachycardia and dictating the therapeutic approach

In spite of the above diagnostic dilemmas when the patient with an acute myocardial infarction suddenly develops a tachycardia at a rate of about 180 per minute with broad QRS complexes displayed on the cardiac monitor and the tachycardia is complicated by either severe

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In spite of the above diagnostic dilemmas when the patient with an acute myocardial infarction suddenly develops a tachycardia at a rate of about 180 per minute with broad QRS complexes displayed on the cardiac monitor and the *tachycardia* is complicated by either severe

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hypotension, heart failure, or perhaps angina the clinician or the specially trained nurse administers emergency therapy As a rule this takes the form of intravenous lidocaine followed by external countershock if necessary He or she may waste no time in a detailed analysis of the ECG in search for subtle changes that might indicate the tachycardia to be supraventricular with aberrancy rather than ventricular in origin nor do they postpone therapy to consider the etiology of the underlying heart disease nor attempt to unravel the basic electrophysiologic mechanism responsible for the initiation and perpetuation of the arrhythmia This nonspecific therapeutic approach may be imperative for two reasons (1) to reverse or prevent the hemodynamic deterioration which may be characterized by shock heart failure and angina and (2) to prevent deterioration of the VT into ventricular fibrillation In fact, these are two prime reasons for prompt initiation of a form of therapy which in itself may have serious and perhaps potentially lethal side effects In patients with supraventricular tachycardia the hemodynamic state usually determines the urgency of therapy, while in VT the possibility of ventricular fibrillation and sudden death is an added risk

However when the VT is not life threatening or fails to respond to the initial therapy, or is recurrent, then the approach to the arrhythmia must be all inclusive It should include a consideration of (1) the etiology of the underlying heart disease and particularly the initiating and precipitating factors (2) the basic electrophysiologic mechanism of the arrhythmia (3) the hemodynamic sequelae and (4) the potential risk of ventricular fibrillation All of these factors determine the ultimate approach to therapy

It is reasonable to assume that in any given patient, VT is an expression of significant organic disease The most common causes for VT are ischemic heart disease particularly acute myocardial infarction, digitalis intoxication and cardiomyopathy of differing etiologies Less commonly, VT may be due to heart failure, per se and specifically due to stretch of the Purkinje fibers and hypoxia Acute precipitating factors may include mechanical stimulation of the ventricle by a dislodged central venous catheter or flow directed catheter, administration of excessive amounts of anti arrhythmic agents or electrolyte disturbances such as hypokalemia, hypoxia, or acid base disturbance If no reasonable mechanical or metabolic explanation for the recurrent arrhythmia can be found in a patient with myocardial infarction the possibility of a ventricular aneurysm might be entertained. VT has also been described in patients with prolapse of the mitral valve leaflet, and in patients with idiopathic prolongation of the QT interval with or without associated deafness The literature also contains isolated reports of patients manifesting VT in whom no evidence of organic cardiac disease was found These cases however, are suspect unless the ECG records show unequivocal fusions and captures or the diagnosis is confirmed by His bundle electrocardiography

The two most commonly considered electrophysiologic mechanisms of VT are re entry and enhanced automaticity Differentiation of these mechanisms from the surface ECG is difficult and most often impossible Despite these limitations there are other features recognizable from the surface ECG which are known to be associated with potential risk of VT and ventricular fibrillation These include premature ventricular complexes with the R on T phenomenon bradycardia in specific settings such as inferior infarction or chronic complete heart block and prolongation of the QT interval which would permit a late and otherwise benign ventricular ectopic impulse to fall during the vulnerable period of recovery and potentially result in VT and ventricular fibrillation

The therapy of VT depends largely upon the clinical setting in which it develops and less so on the suspected electrophysiologic mechanisms In the emergency situation, conversion is most often attempted with lidocaine and countershock if necessary If these prove unsuccessful procainamide or quinidine may be given Once the VT is terminated, or in the nonemergent situation, the approach may be directed to correction of the contributing factors referred to earlier For long term prophylactic use quinidine or procainamide are usually the drugs of choice Certain other anti arrhythmic agents are useful in specific situations For example in digitalis intoxication potassium or diphenylhydantoin may prove the drug of choice Similarly propranolol may prove an effective anti arrhythmic agent during the early hours of acute myocardial infarction when ventricular arrhythmias may be

due to excessive release of catecholamines Drug combinations are employed on an empirical basis since neither the precise electrophysiologic mechanism responsible for most ventricular tachycardias nor the exact mechanism of action of anti arrhythmic drugs are known Ventricular pacing may be used in an attempt to suppress recurrent and otherwise refractory VT Infrequently ventricular aneurysmectomy may be justified when the aneurysm is thought to perpetuate the VT Preliminary scattered reports of disappearance of recurrent VT following aorto coronary bypass surgery have appeared in the literature

It appears from the foregoing that the diagnosis and therapeutic approach to VT must be based on all available laboratory and clinical information In fact, the diagnosis may at times be more secure if not deduced solely on the basis of clinical information Although suppression of isolated, acute episodes of VT by presently available therapeutic interventions is as a rule successful long range suppression of ventricular ectopic arrhythmias is more difficult This is partly due to the multitude of variables responsible for the arrhythmia and serious shortcomings of presently available anti arrhythmic agents

Clinical communications

The angiotensin infusion test as a method of evaluating left ventricular function

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It is very difficult to accurately quantitate left ventricular function in the clinical cardiac laboratory One method proposed has been to gradually increase ventricular afterload by the graded infusion of angiotensin plotting the response of left ventricular stroke work to increasing left ventricular end diastolic pressure [1] For a given increase in left ventricular end diastolic pressure, a better ventricle would be expected to generate a larger ventricular stroke work than would a poorly functioning ventricle This method has been used both in cardiac research and in clinical cardiac catheterization laboratories [2,4] However recent work has shown that there may be no constant relationship between left ventricular end diastolic pressure and stroke work index in intact conscious dogs who have been given graded infusions of angiotensin [5] The purpose of this paper is to evaluate the response of the myocardium to ventricular afterload by the angiotensin infusion method in patients with and without coronary disease and to compare the ventricular function curves between the two groups

Materials and methods

Fifteen patients undergoing coronary arteriography were divided into two groups, depending on whether or not they had arteriographic evidence of coronary disease

Seven patients (Group 1) were suspected of having coronary artery disease but their coronary arteriograms were normal There were two men and five women aged 17 to 55 with a mean age of 37 years Six of the patients had chest pain probably of musculoskeletal or gastrointestinal origin but without any evidence of heart disease One patient (MFD) was an entirely asymptomatic 17 year old female with electrocardiographic T wave inversions left axis deviation and a family history suggestive of primary myocardial disease Her physical examination coronary arteriogram and intracardiac pressures were entirely normal

Group 2 consisted of eight patients with chest pain and coronary artery disease proven by coronary arteriography Three patients had total occlusion of at least one major coronary artery (RC EJ and WL) four had greater than 50 per cent narrowing in two or more arteries (JG IG HJ, and CS) and one patient had mild but diffuse narrowing of the anterior descending artery (JB) All eight patients were men ranging in age from 47 to 63 the mean age was 55 years Two of the patients (IG and EJ) had had a previous myocardial infarction the remaining six patients had angina pectoris Five patients were Functional Class II (New York Heart Association Classification) two patients were Functional Class III and one patient was Functional Class IV—in all instances the limiting symptom was angina A fourth heart sound was heard in seven subjects and a third heart sound in six subjects Left ventricular or left atrial size was not increased on x ray in any subject and there was no

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Table I Effects of angiotensin infusion in patients in Group 1 without coronary disease

Patient	*Age*	*Sex*	*Infusion rate*	*Heart rate*	*Arterial pressure S/D*	*LVEDP*	*CI*	*SVI*	*SWI*
MFD	17	F	0	92	95/65	8	3.28	35	39.0
			1.0	92	120/90	14	2.51	27	41.6
			2.0	90	135/95	19	3.09	31	44.5
MD	47	F	0	78	123/70	8	3.54	45	61.0
			2.0	66	148/85	17	2.85	43	72.5
			4.0	60	178/100	23	2.78	46	80.8
HP	30	M	0	90	140/80	9	2.66	30	47
			1.5	75	148/85	14	2.04	27	42.9
			2.0	72	148/92	14	1.95	27	47.2
TE	50	F	0	114	128/78	6	2.62	23	33
			4.0	96	152/85	14	2.61	27	43.5
			6.0	99	174/102	20	2.32	23	42.4
DT	31	M	0	90	120/75	10	4.23	47	60.4
			2.5	77	155/95	20	3.82	50	79.4
			3.0	78	170/96	24	3.79	49	82.6
RV	33	F	0	72	115/68	12	4.22	59	83.2
			2.0	69	165/90	20	3.28	48	86.5
RD	55	F	0	102	166/82	11	3.81	37	67.5
			2.0	84	192/94	20	3.22	38	81.8
			3.0	84	205/100	25	2.77	33	63.9

radiologic evidence of heart failure None of the subjects had mitral regurgitation Normal sinus rhythm was present in all subjects The resting 12 lead electrocardiogram was normal in four subjects and in one subject the only abnormality was PR interval prolongation to 0.29 second. One subject had left axis deviation The two patients who had had previous myocardial infarction had nonspecific S T T wave changes but no diagnostic Q waves

The patients were premedicated with 75 mg of pentobarbital and 75 mg of meperidine approximately two hours before the angiotensin infusion began Right and left heart catheterization was performed in all subjects Arterial pressure was measured through a brachial arterial needle Cardiac output was determined by the indicator dilution technique (indocyanine green dye) with injection in the left ventricle and withdrawal from the brachial artery The angiotensin infusion test was done before left ventriculography or coronary artery angiography according to the following protocol Cardiac output, as well as left ventricular systolic end diastolic (LVEDP) and brachial arterial pressures were determined at rest Brachial arterial pressure LVEDP and heart rate were monitored continuously during the infusion Angiotensin was given slowly intravenously beginning at an infusion rate of 1.0 mcg per minute and gradually increasing the dose by 0.5 mcg per minute to 1.0 mcg per minute increments every four to five minutes When the LVEDP rose at least 5 to 10 mm Hg the cardiac output and pressure measurements were repeated In 12 of the subjects the measurements were repeated a second time at a higher infusion rate and a higher LVEDP in order to have three points on the function curve At each level of infusion rate care was taken to insure that the pressures had reached a plateau and were stable for at least five minutes before the cardiac output was determined. The brachial arterial and left ventricular pressures were rechecked after each cardiac output determination and the patient was considered to be in a steady state and acceptable for the study only if the pressures before and after the output determinations were similar At peak LVEDP the infusion rate ranged from 1.0 mcg per minute to 6.0 mcg per minute with an average of 2.4 mcg per minute Fourteen of the fifteen subjects received a peak angiotensin infusion rate of 3.0 mcg per minute or less The duration of angiotensin infusion averaged 21 minutes

Left ventricular stroke work index (LVSWI) in gram meters per square meter was calculated by the formula

$$\text{LVSWI} = \frac{\text{SVI} \times (\text{LVS} - \text{LVEDP}) \times 1.36}{100}$$

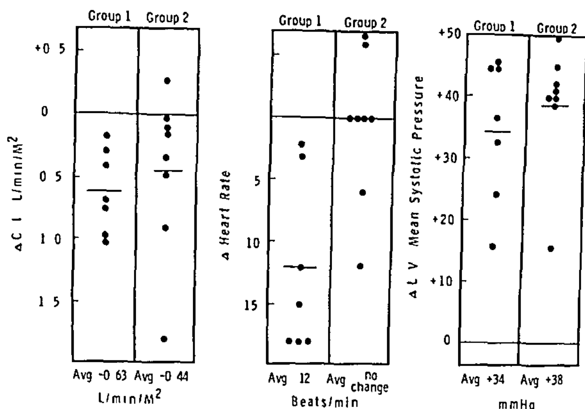


Fig 1 Peak change in cardiac index (CI) heart rate and left ventricular mean systolic pressure during the infusion of angiotensin Dots indicate individual patients Transverse line indicates the mean value for that group

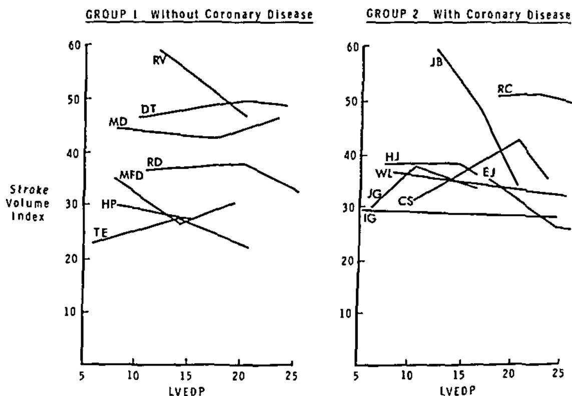


Fig 2 Relationship between stroke volume index (in milliliters per square meter) and left ventricular end diastolic pressure (in millimeters of mercury) before and during increasing rates of angiotensin infusion.

in which SVI represents the stroke volume index in milliliters per square meter LVS represents the mean left ventricular systolic pressure in millimeters of mercury determined by integrating the left ventricular pressure during the ejection period, and LVEDP represents left ventricular end diastolic pressure Normal values for cardiac index were 2 5 to 5 0 L per minute per

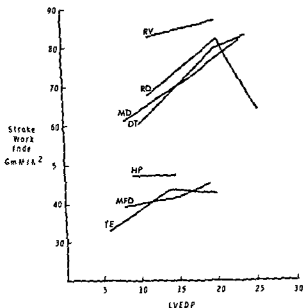


Fig 3 Relationship between stroke work index (in gram meters per square meter) and left ventricular end diastolic pressure (in millimeters of mercury) before and during increasing rates of angiotensin infusion in seven patients without coronary artery disease

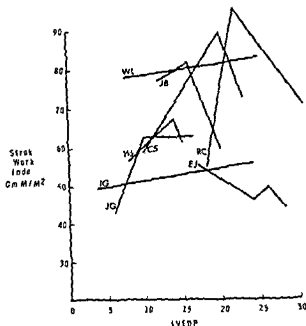


Fig 4 Relationship between stroke work index (in gram meters per square meter) and left ventricular end diastolic pressure (in millimeters of mercury) before and during increasing rates of angiotensin infusion in eight patients with coronary artery disease

square meter and for LVEDP ≤12 mm Hg The zero level for the Statham P23 Dd pressure transducers was 5 cm below the sternal angle

Results

Group I Patients without coronary disease (Table I) All seven patients had normal LVEDP and cardiac index at rest During angiotensin infusion the average increase in left ventricular mean systolic pressure was 34 mm Hg (Fig 1) The cardiac index decreased in all patients (average 0 63 L per minute per square meter) The heart rate decreased in all subjects an average of 12 beats per minute The stroke volume index (Fig 2) increased slightly in two patients decreased in four patients and in one patient there was an initial increase but a return to the baseline value as the LVEDP rose The stroke work index rose in three subjects (RV MD and DT in Fig 3) One patient (RD) showed initial increase but then a fall at higher left ventricular end diastolic pressures In three subjects (HP MFD and TE) there was little or no increase in SWI as the LVEDP rose and the peak level attained was quite low

Group II Patients with coronary disease (Table II) Six of the eight patients had normal LVEDP at rest but in two subjects it was elevated (EJ and RC) The resting cardiac index was normal in all subjects During angiotensin infusion the average increase in left ventricular mean systolic pressure was 38 mm Hg (Fig 1) The cardiac index fell in seven of the eight patients The average reduction for the entire group was 0 44 L per minute per square meter The heart rate remained unchanged in four patients was increased in two patients and was decreased in two patients The stroke volume was diminished in six patients and increased in two patients (Fig 2) In five patients the SWI initially rose in response to angiotensin but as the LVEDP continued to rise the SWI declined (Fig 4) One patient (WL) had a normal SWI response to angiotensin—he had three vessel coronary disease with total occlusion of the right coronary artery 50 per cent narrowing of the circumflex artery and diffuse narrowing of the anterior descending artery Two subjects (IG and EJ) had little or no increase in stroke work after angiotensin

Discussion

There is a significant body of evidence that angiotensin causes a decrease in myocardial contractility Many investigators have shown that

Table II Effects of angiotensin infusion in patients in Group 2 with coronary disease

Patient	Age	Sex	Infusion rate	Heart rate	Arterial pressure S/D	LVEDP	CI	SVI	SWI
JB	63	M	0	72	134/60	12	4 21	59	76 4
			1 0	66	163/79	16	3 23	49	81
			2 0	72	175/83	20	2 41	34	58 4
RC	58	M	0	66	115/60	18	3 41	51	53 5
			2 0	66	180/95	22	3 42	51	94 3
			3 0	60	170/90	28	2 94	49	77 2
JG	53	M	0	90	120/80	6	2 73	30	43 5
			1 0	90	145/85	10	3 37	38	62 2
			2 0	90	170/100	16	3 00	34	62 2
IG	58	M	0	93	140/80	4	2 90	30	49 6
			2 0	102	195/100	24	2 87	28	55 3
HJ	57	M	0	78	110/60	8	2 95	38	56
			0 67	78	155/80	14	2 97	38	67
			1 2	78	155/80	16	2 83	36	61
EJ	53	M	0	78	158/85	17	2 72	35	55
			1	84	177/100	24	2 20	26	45 6
			1 5	84	192/108	26	2 20	26	48 7
			2	84	203/118	28	1 82	22	43 8
WL	56	M	0	81	190/85	8	2 96	36	77 6
			1 0	81	220/105	25	2 62	32	82 3
CS	47	M	0	90	160/92	10	2 86	32	58 9
			1 0	78	180/104	20	3 34	43	87 8
			1 5	78	196/112	23	2 70	35	72

angiotensin decreases cardiac output in the intact animal and human[6,16] This reduction may be related to the bradycardia which usually accompanies angiotensin[6,7,12,15] However in some instances a decrease in stroke volume may accompany the slower heart rates and would indicate depressed myocardial contractility[8,11] In the intact conscious dog angiotensin causes a decrease in stroke excursion and an increase in ventricular size at end systole and end diastole[5] In the functionally intact cat myocardial depression has been observed in some instances during and after angiotensin infusion[17] On the other hand the direct action of angiotensin on the isolated papillary muscle produces a positive inotropic response[18,19] The contrast is striking between the response to angiotensin in intact animal models and in isolated papillary muscle preparations and suggests that the overall effect of the drug is the sum of both its direct and indirect effects

The effect of angiotensin on the myocardium in the intact animal is partially a reflex one Increases in arterial pressure produce a negative inotropic effect on the ventricle through the carotid sinus baroreceptors[20] Since all of our normal subjects developed a decrease in heart rate after angiotensin, it would appear that the baroreceptor reflex arc was intact However even in the face of a slower heart rate, stroke volume was decreased in five subjects, and increased only slightly in two subjects In only three subjects was there any appreciable increase in stroke work These responses would indicate a decrease in contractility

Previous reports have shown variability in the response of the ventricle to angiotensin Downing and Sonnenblick[17] reported myocardial depression in some cats during the angiotensin infusion and in about one third of the cats after infusion O'Rourke Pegram and Bishop[5] reported a marked variability in the function curves from dog to dog and even in the same dogs from day to day during angiotensin administration A decrease in contractility in normal dogs was common In our patients there was no predictable response regardless of whether they were normal or had coronary artery disease Many of the patients who clearly had no cardiac pathology had function curves which were not as steep as those of other patients with coronary artery disease

The effects of angiotensin on the coronary ar

teries may play a role in depressing the myocardium Just as angiotensin causes peripheral arterial constriction so too it affects the coronary circulation [10,19,21] and this may secondarily affect myocardial contractility in the intact subject Simultaneous observations of myocardial contractility and coronary blood flow during angiotensin infusion have demonstrated that the depression of myocardial contractility coincided with the decrease in coronary blood flow [17]

Finally reduction in stroke volume can result from the mechanical effects of increased afterload due to angiotensin In the isolated papillary muscle preparation when increasing afterloads are applied to the muscle work progressively increases up to a maximum point beyond which there is a decrease in work performed.[22] In the areflexic cat, progressive increases in mean aortic pressure from 75 to 120 mm Hg produce progressive increases in stroke volume and stroke work At higher levels of mean aortic pressure (150 mm Hg) stroke volume diminishes Whether or not the afterload achieved during infusion of angiotensin in our patients was large enough to depress stroke volume is unknown However the aortic diastolic pressures ranged from 90 to 102 mm Hg at peak angiotensin infusion in the normal subjects and that level of pressure is not likely to be beyond the capacity limits of the ventricle

The variability of response and the frequent negative inotropic effects of angiotensin in our patients are quite similar to the animal experiments of Downing and Sonnenblick[17] and of O Rourke Pegram and Bishop [5] In ventricular function testing whatever physiologic stress is used to test the myocardium must have neither an enhancing nor an inhibiting effect on the myocardium itself It appears that the negative inotropic effect associated with angiotensin administration in intact man mitigates against its usefulness in evaluating ventricular function Because it increases coronary artery resistance it would seem particularly unsuited to patients with coronary artery disease

Summary

Fifteen patients had left ventricular function measured by the angiotensin infusion method. Seven patients had no evidence of heart disease and eight patients had angina pectoris and coronary arteriographic evidence of coronary disease without congestive heart failure During angiotensin infusion those patients without heart disease had a decrease in cardiac index (average 0 63 L per minute per square meter) and a decrease in heart rate (average 12 beats per minute) The ventricular function curve had a poor SWI response in four of the seven subjects. The patients with coronary artery disease also had a reduction in cardiac index during angiotensin (average 0 44 L per minute per square meter) and the heart rate was unchanged in four subjects increased in two subjects and decreased in two subjects. Six of the subjects had flat or descending slopes on the function curve and in one subject there was only a very gradual ascending slope Many of the curves of both groups looked similar so that the function curves did not differentiate between those patients with or without heart disease

The mechanism for production of bradycardia reduction of cardiac output and depressed function curves with angiotensin is multifactorial but is probably due to the baroreceptor reflex response the increase in coronary artery resistance and possibly to the direct effect of increased left ventricular afterload itself

The ventricular response to angiotensin is so variable that the angiotensin infusion method of evaluating ventricular function is not reliable

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Coronary artery anatomy before and after direct revascularization surgery: clinical and cinearteriographic studies in 67 selected patients

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The development of surgical techniques for direct revascularization of the native coronary arterial circulation has had a major impact on clinical management of coronary heart disease. In our experience, previously intractable chronic angina pectoris has been abolished or rendered susceptible to satisfactory medical control in the vast majority of surgically treated patients.[1] Surgical mortality has ranged between 0.8 per cent[1] and 15 per cent, with an average of about 6 per cent,[3] depending on a variety of factors including patient selection. Patency rate of saphenous vein grafts one year after operation has been reported to vary from 66 per cent[4] to 82 per cent.[5] A higher patency rate has been observed with internal mammary artery grafts.[6] A few reports, including a preliminary communication from this laboratory,[4,7,9] have suggested that obstructive lesions may progress more rapidly in coronary arteries to which venous bypass grafts have been attached than would be expected in the natural course of the disease. We have now had the opportunity to perform postoperative angiograms in 67 selected patients who underwent direct coronary revascularization surgery at the Peter Bent Brigham Hospital prior to July, 1972. Analysis of observed changes in the arteriographic anatomy of grafted and nongrafted vessels forms the basis for this report.

Methods

Direct coronary revascularization surgery for incapacitating angina pectoris was performed in 202 patients at the Peter Bent Brigham Hospital from July, 1970, to July, 1972. Sixty-seven patients (60 men and 7 women, mean age 48 years) were evaluated at the laboratories of the Cardiovascular Division before and after surgery and constitute the study group. Of the 67 patients

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The development of surgical techniques for direct revascularization of the native coronary *arterial circulation* has had a major impact on clinical management of coronary heart disease In our experience previously intractable chronic angina pectoris has been abolished or rendered susceptible to satisfactory medical control in the vast majority of surgically treated patients [1] Surgical mortality has ranged between 0 8 per cent[1] and 15 per cent[2] with an average of about 6 per cent [3] depending on a variety of factors in cluding patient selection Patency rate of sa phenous vein grafts one year after operation has been reported to vary from 66 per cent[4] to 82 per cent [5] A higher patency rate has been observed with internal mammary artery grafts [6] A few re ports including a preliminary communication from this laboratory[4 7 8] have suggested that obstructive lesions may progress more rapidly in coronary arteries to which venous bypass grafts have been attached than would be expected in the natural course of the disease We have now had the opportunity to perform postoperative an giograms in 67 selected patients who underwent direct coronary revascularization surgery at the Peter Bent Brigham Hospital prior to July 1972 Analysis of observed changes in the arterio graphic anatomy of grafted and nongrafted vessels forms the basis for this report

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Methods

Direct coronary revascularization surgery for incapacitating angina pectoris was performed in 202 patients at the Peter Bent Brigham Hospital from July 1970 to July, 1972 Sixty seven pa tients (60 men and 7 women mean age 48 years) were evaluated at the laboratories of the Cardio vascular Division before and *after* surgery and constitute the study group Of the 67 patients

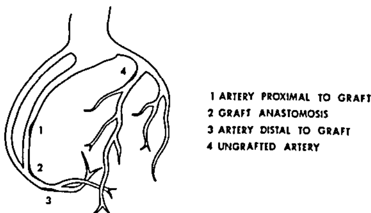


Fig 1 Schema for localization of new obstructive lesions in coronary arteries following bypass surgery Operated arteries were divided into three segments relative to the site of anastomosis (1) proximal (2) anastomotic and (3) distal Progression in nonoperated arteries is also represented [4]

only six had angina of equal or greater severity (NYHA Classes III and IV) than prior to surgery 19 were completely asymptomatic and had not sustained postoperative infarction, 39 had mild to moderate anginal symptoms (NYHA Classes I and II), and three were free of angina following postoperative myocardial infarction To serve as a control group for frequency and severity of postoperative angina the 135 patients (120 men and 15 women mean age, 50 years) who were not restudied were queried relative to their clinical state with a standard interview by a staff physician or by a mailed questionnaire Follow up was obtained in 134 patients (99 per cent) Mean interval between the first catheterization and surgery was 1 3 months and mean interval from operation to second catheterization was 12 6 months Pre and postoperative evaluation included inquiry relative to a history of cigarette smoking chest pain and congestive heart failure presence of hypertension and of lipid or carbohydrate abnormalities resting electrocardiogram selective left ventriculography and selective cineangiography of each coronary artery and each graft vessel (All native arteries and graft vessels were visualized in several projections to obtain a cross sectional representation of the vessel lumen) Standard techniques previously reported from this laboratory were used throughout the study [10,11]

Surgical technique of coronary bypass grafting All operations were performed through a standard median sternotomy exposure Cardiopulmonary bypass with total hemodilution (hematocrit averaged 20 volumes per cent) moderate hypothermia (28 to 30° C) ventricular fibrillation and left ventricular decompression was used in all cases Right coronary anastomoses were performed with the artery occluded by proximal and distal atraumatic silicone elastomer tapes Most anastomoses to branches of the left coronary system were performed with periods of aortic occlusion (up to 15 minutes) with tapes used only occasionally Mechanical arterial dilation was used sparingly and gently with no effort to actually enlarge the arterial lumen The veins for use as grafts were taken from the greater saphenous system between the groin and knee in all patients Branches were ligated and the veins harvested through a series of small incisions In most cases no heparin was given before or during vein removal Veins were irrigated and gently distended with heparinized lactated Ringer s solution Adventitia was undisturbed whenever possible and anastomoses were performed as distant as possible from the closest valve Venous and aortic anastomoses were performed with running suture of siliconized polyester material

Distal endarterectomy was accomplished where needed by manual techniques without gas insufflation Clearing of the proximal artery was avoided to obviate competitive flow for the vein graft In those patients with pedicle grafts of internal mammary artery to left anterior descending artery anastomoses were performed with interrupted fine polyester sutures

Coronary arteriograms Analysis of changes in coronary arterial anatomy was performed by simultaneous evaluation of pre and postoperative selective cineangiograms of coronary arteries and grafts Lesions were localized as follows the grafted coronary artery was divided into three segments proximal to the anastomosis, at the site of anastomosis and distal to the anastomosis (Fig 1) *Proximal lesions* included lesions between the coronary ostium and the site of graft anastomosis (Fig 2) and lesions at the site of anastomosis which were contiguous with a proximal obstruction *Anastomotic lesions* were defined as lesions at the site of anastomosis not associated with contiguous proximal or distal obstruction (Fig 3) *Distal lesions* were defined as lesions distal to the site of anastomosis and separated from the site of anastomosis by a segment of normal artery lumen at least 1 cm long (Fig 4) A lesion distal to the site of anastomosis but contiguous with the anastomosis was considered to have an indeterminate site of origin

Progression of stenotic lesions Progression

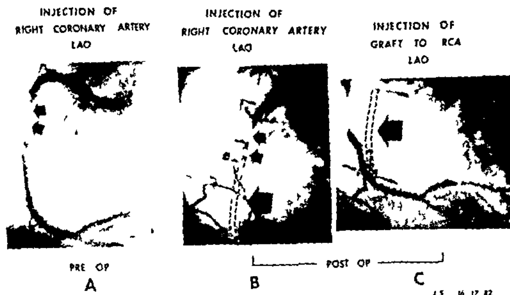


Fig 2 Proximal progression in the RCA (A) Preoperative angiogram. Arrows indicate stenosis. (B) Postoperative injection of the native RCA Note the loss of a long proximal segment of artery (large arrow) (C) Postoperative injection of the bypass graft. The nonvisualized proximal segment of the RCA is drawn for orientation (large arrow)

was defined as (1) change to total obstruction (2) increased narrowing of a prior stenosis to 75 per cent or more of lumen diameter and/or (3) development of a new lesion of greater than 50 per cent of normal lumen diameter in either operated or nonoperated coronary arteries (Fig 5)

Progression of obstructive disease was evaluated by comparing the number of arteries exhibiting progression at the postoperative study to the total number of grafted and ungrafted arteries studied up to that point in time following surgery The true rate of progression can be documented with certainty only by multiple angiographic studies on the same patients This is often not feasible in the human subject However a minimum progression rate could be derived based on a simple sampling technique by dividing the number of vessels exhibiting progression by the number of vessels studied. Since multiple events cannot be detected by this technique the true rate of progression must be higher if it differs from the calculated minimum progression rate

Graft angiography Opacification of every graft or the blind outpocket from the aorta of an occluded graft vessel allowed the determination of graft patency or occlusion to be made Per cent graft occlusion was determined by the ratio of the total number of grafts occluded to the total

Table I Clinical status of 201 patients following coronary artery bypass surgery

	Study group (67)		*Control group (134)*	
	No	*Per cent*	*No*	*Per cent*
No angina	22	33	68	51
Angina (NYHA Classes I and II)	39	58	53	40
Angina (NYHA Classes III and IV)	6	9	6	4
Deceased	—	—	7	5

Three had seve e angina pr or to death

number of grafts studied at any point in time No attempt was made to correlate patency with diameter or condition of recipient artery or the surgeon s estimate of the technical difficulty of performing the anastomosis

Lipid analysis Blood lipid analysis was determined by serum electrophoretic methods described previously [12] Patients were classified as normal Type II or Type IV

Results

Postoperative clinical status Table I indicates that in the current series more patients in the control group were free of angina than in the

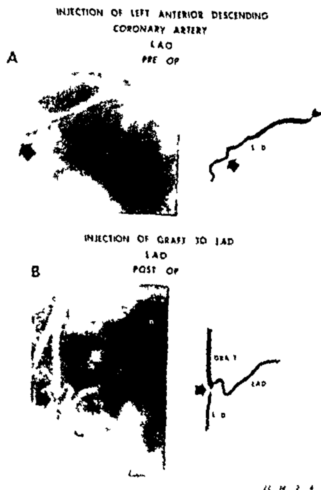


Fig 3 Progression at site of anastomosis in LAD (A) Preoperative injection of native artery shows site of anastomosis (arrow) is free of obstructive lesions (B) Injection of graft to LAD The graft is patent and fills proximal and distal segments of the artery Note lesion at site of anastomosis (arrow)

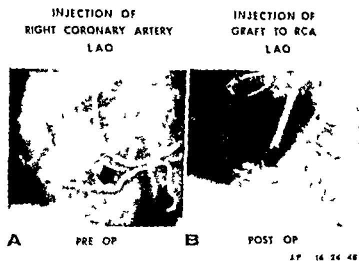


Fig 4 Distal progression in the RCA (A) Preoperative angiogram Arrow indicates site of subsequent progression (B) Postoperative injection of patent graft The nonvisualized proximal artery segment is drawn for orientation There is a new total obstruction of the posterior descending branch after the bifurcation *(large arrow)* Note the separation of this distal lesion from the site of anastomosis (bottom arrow)

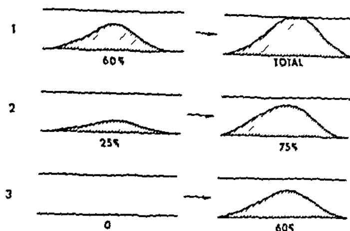


Fig 5 Postoperative arterial disease Criteria for progression of obstructive lesions are illustrated. See text for explanation

study group This difference was statistically significant ($p < 0.05$) Ninety one per cent of both groups were improved from their preoperative status In the study group the time course for recurrence of angina following surgery (Fig 6) reveals that the majority of patients noted return of angina in the first four to six months after operation All symptomatic patients had either nonpatent grafts or progression in operated or nonoperated coronary arteries.

Grafts and patency One hundred and sixteen arteries had angiographic evidence of significant disease One hundred and twelve arteries were considered operable at the time of surgery These 112 coronary arteries received 115 grafts (Three patients who had bypass grafts to the left anterior descending coronary artery also had grafts to the first diagonal branch of the left anterior descending artery) There were 112 saphenous vein and three internal mammary artery bypass grafts performed The distal segments of the 112 grafted arteries exhibited atherosclerotic disease with 34 patients having lesions of 50 per cent obstruction and nine patients with less than 50 per cent obstruction A total of 89 arteries were not operated upon As noted earlier, four diseased arteries were assessed by the surgeon to be inoperable, while 64 arteries exhibited no arteriographic evidence of atherosclerosis and 21 arteries were considered to have hemodynamically insignificant lesions

The overall graft patency rate was 58 per cent Twenty two of the 46 nonpatent grafts were in arteries exhibiting distal lesions in the preoperative study, including 11 with lesions of approximately 50 per cent There was no significant

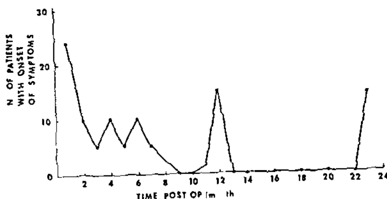


Fig 6 Onset of symptoms relative to time following operation. Severe angina was experienced by only 9 per cent of patients in the study group and 7 per cent of the patients in the control group

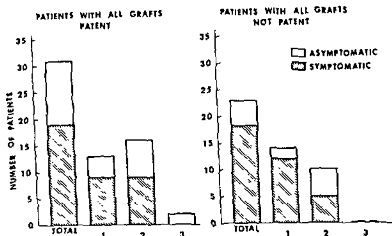


Fig 7 Relationship of return of symptoms following surgery to graft patency (A) Eighteen patients with all grafts patent had mild angina (B) Six *patients with all grafts* occluded were asymptomatic although three pa tients sustained postoperative myocardial infarction

difference among graft patency rates for the three coronary arteries

Status of grafts in relation to symptoms The relationship between postoperative symptoms and patency of bypass grafts is shown in Table II The graft patency rate was 74 per cent in a symptomatic patients 60 per cent in patients with mild to moderate angina and 10 per cent ($p < 0.05$) in patients with severe angina Total graft patency rate was 65 per cent in the 58 pa tients who were improved after surgery and at least one graft was patent in 52 of the 58 (90 per cent)

All grafts were patent in 31 of the 67 patients *in this* study None of the 31 patients had severe angina following surgery 13 were asymptomatic and 18 had mild angina (Fig 7) Only two of the latter 18 patients had incomplete revasculariza tion In both cases the distal circumflex artery could not be bypassed for technical reasons despite the presence of a high grade proximal *stenosis* Of *23* patients with no grafts patent only six were free of angina (Fig 7) and three of these six patients sustained a postoperative myocardial infarction at two days three days and three months respectively There was no sig nificant difference in the time or the frequency of return of symptoms between patients with single or double grafts

Graft occlusion rate Irrespective of patient status the per cent graft occlusion rate in *this* selected series was 42 per cent (Fig 8) The num ber of graft occlusions formed a fixed percentage of the total grafts studied at any time after the fourth postoperative month

Progression in unoperated arteries Twelve of

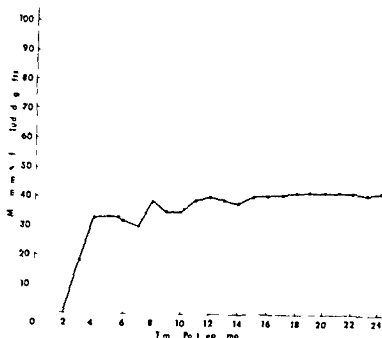


Fig 8 Graft occlusions relative to time of postoperative study

Table II Relationship between postoperative symptoms and graft patency

	No of patients	*No of grafts*	*No. of patent grafts*	*No. of nonpatent grafts*
Asymptomatic	19	38	28 (74%)	10
Asymptomatic s/p myocardial infarction	3	4	0	4
Mild angina pectoris (≤ NYHA Class II)	39	63	38 (60%)	25
Severe angina pectoris (≥ NYHA Class III)	6	10	1 (10%)	9
Total	67	115	67 (58%)	48

At least one graft was patent in 52 out of the 58 patients improved after surgery

89 (14 per cent) unoperated arteries met our criteria for progression Only two of these 12 arteries had new total occlusion (Fig 9) These two coronary arteries had minimal nonobstructive pre existing disease and did not differ from the other unoperated arteries with progression

Progression in operated arteries

A Total Sixty four out of 112 (57 per cent) arteries receiving a graft exhibited a change in lumen at some site (usually proximal to the anastomosis) compared to only 12 out of 89 (14 per cent) unoperated arteries ($p < 0.01$) Of the 12 unoperated arteries with progression only two arteries developed total obstruction both in the proximal third (Fig 9) In the group of 44 grafted arteries that developed total obstruction following surgery 35 arteries were occluded proximal to the site of anastomosis and nine were occluded distal to the anastomosis By the fifth month following surgery there was a constant minimal rate of over all progression equal to a fixed percentage of operated coronary arteries studied (Fig 10) Progression of obstructive lesions occurred at one or more sites in 40 out of 67 (60 per cent) vessels with patent grafts and in 24 out of 48 (50 per cent) vessels with nonpatent grafts (P = NS) (Fig 11)

B Segmental The rate of progression differed for each region of the operated coronary artery proximal progression occurred in 37 per cent of grafted arteries New obstructive lesions at the site of anastomosis occurred in 10 per cent of grafted arteries (Fig 10) Nineteen out of 112 (17 per cent) grafted coronary arteries had new distal lesions separated from the site of anastomosis by a 1 cm segment of normal artery lumen There were three additional new lesions located within 1 cm. downstream from the site of anasto

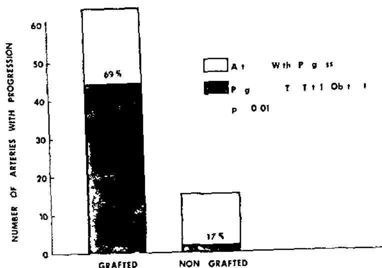


Fig 9 Progression to total obstruction Operated arteries progressed to total obstruction with far greater fre quency than nonoperated arteries

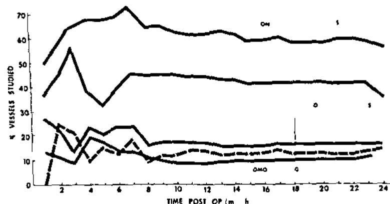


Fig 10 Minimal progression rates for segments of arteries receiving grafts Operated vessels have a fourfold higher prevalence of progression than nonoperated vessels Note similar progression rate for unoperated arteries and distal segments of operated arteries.

mosis and contiguous with the site of anastomos is Even if these three lesions with an indetermi nate site of origin were included among new dis tal lesions, the prevalence rate for new distal obstructions increased only to 20 per cent and is not significantly different from the progression rate for unoperated arteries (14 per cent)

The prevalence and location of segmental progression was independent of graft patency (Fig 11) The frequency of segmental progression for the 19 patients who were asymptomatic was independent of graft patency The frequency of segmental progression for the 13 asymptomatic patients with all grafts patent and for the six pa tients with persistent or recurrent severe angina pectoris was identical to the entire study group

Progression and peri or postoperative myocar dial infarction In seven patients with new Q waves suggestive of peri or early postoperative myocardial infarction seven out of 13 grafts were occluded Eleven out of 13 grafted arteries exhibited proximal progression and three ex hibited progression distal to the anastomosis In the two patients with late postoperative myocar dial infarction three out of three grafts were oc cluded and all three grafted coronary arteries exhibited progression proximal to anastomosis

Effect of endarterectomy on graft patency and progression A total of 18 right coronary arteries and one left anterior descending artery under went endarterectomy in conjunction with saphenous vein bypass Eleven of these 19 (58 per

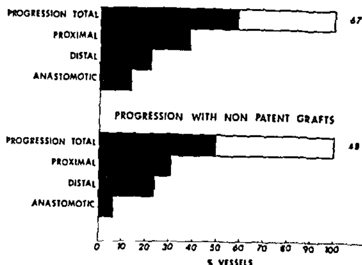


Fig 11 Progression in native coronary arteries relative to graft patency The frequency of overall and regional progression is independent of graft patency

cent) vessels had patent grafts and 12 of these 19 (63 per cent) coronary arteries exhibited progression In this small experience the rate of graft obstruction and progression in this subgroup of operated coronary arteries did not differ significantly from the total group of operated arteries in overall frequency (63 per cent vs 57 per cent) or in the distribution of segmental lesions proximal or distal to the anastomosis

Progression and preoperative risk factors Clinical evaluation of risk factors including lipid abnormalities, diabetes mellitus, hypertension, history of congestive heart failure, and prior or persistent smoking did not correlate with return of angina pectoris graft patency or progression of obstructive coronary artery lesions

Discussion

The efficacy of direct aortocoronary bypass surgery to relieve angina pectoris in patients with coronary artery disease may be limited by the fact that (1) the graft can close (2) arteries served by a graft can be adversely affected by the graft and its flow (3) ungrafted arteries can undergo advancement of the underlying atherosclerotic process (4) revascularization may be incomplete and ischemia persist in a patchy fashion and of course, (5) angina of significant severity may occur in the absence of angiographically demonstrable obstruction demonstrating that a certain incidence of angina may conceivably occur even with complete revascularization It is not known if changes occur in specific settings relative to prior disease states, type of graft and site of anastomosis or if changes are part of a continuum during the biologic life of a graft or occur as a self limited immediate response to a new anatomic and hydraulic condition

Analysis of development of symptoms relative to the number of grafts per patient showed no significant difference in the frequency or time of return of symptoms Patency of all grafts was not more frequently associated with relief of angina than was closure of one or more grafts Patency of grafts to every operated vessel did not, moreover, protect against the return of angina This may be partially explained by the liberal criteria used to select operable arteries at the time of surgery Only four out of 116 arteries were deemed inoperable although distal disease was present in 43 out of the 112 arteries that were subsequently revascularized

The frequency of graft occlusion (Fig 8) became constant by the fourth postoperative month and a maximal patency rate could be defined so that a fixed percentage of the total number of grafts studied at any time was shown to be occluded This patency rate was clearly determined in a preselected population and may *not* represent the patency rate for the total cohort of 202 consecutive patients The total may have been *higher* judging from a higher prevalence of totally asymptomatic patients in the control group

Progression of obstructive coronary lesions was found in one or more regions in 57 per cent of operated coronary arteries The 14 per cent incidence of progression seen in nonoperated arteries in this study group is similar to the rate of natural progression previously reported from this laboratory [13] After the fifth month postoperatively, total and segmental progression occurred at a constant rate 37 per cent of proximal 17 per cent of distal and 10 per cent of anastomotic areas showing increased narrowing or occlusion (Fig 10) None of these rates selectively accrued with time Griffith and co workers[4] and Malinow and co workers[14] have found a similar frequency of progression in the pre graft segment but occurrence of progression far distal to the site of anastomosis has yet to be stressed As outlined above when only distal lesions far removed from the site of anastomosis were considered the prevalence rate for new lesions downstream from the anastomosis was 17 per cent and was not different from the rate for new lesions in unoperated arteries Even if those lesions with uncertain site of origin were considered the total prevalence rate is only 20 per

cent and is not clearly different from the rate for progression in unoperated vessels The addition of manual endarterectomy to saphenous vein bypass surgery neither adversely nor beneficially affected the prevalence of progression or graft occlusion

Hydraulic influences of a functional graft downstream to a stenosis have been investigated in acute animal preparations and theories have been advanced to explain postoperative progression of proximal obstructive lesions Considerable differences have been noted in the partition of blood flow between the graft and the proximal native coronary artery resulting from variations in the relative diameters of these two vessels [15] In the presence of a 70 per cent or greater coronary artery stenosis addition of a downstream graft virtually eliminated all flow across the proximal arterial lesion [16] It was suggested that the relative stasis produced in the proximal segment predisposed to early thrombosis of the vessel In this regard, progression to total obstruction of proximal stenotic vessels has been reported as early as two weeks following surgery [7] The statistical method employed in the present communication also suggests that progression occurs early after surgery The natural advancement of atherosclerotic disease may play a role in the process of proximal progression as well Closure of the proximal segment is probably of little functional consequence provided the life of the graft is not transient and that few proximal tributary vessels are influenced by the occlusive process in the main artery

Lesions at the site of the graft to coronary artery anastomosis (Fig 3) and lesions contiguous with the anastomosis may reflect technical problems incurred at operation or the development of nonatherosclerotic reactive jet lesions

This report documents that significant distal progressive obstructive disease may occur in all three coronary arteries far removed from the site of anastomosis In acute experiments in animal preparations the dominant resistance to blood flow in the coronary artery bypass graft system has been shown to reside in the distal coronary arterial bed.[16] Early closure of the proximal coronary artery makes survival of myocardium dependent upon patency of the graft and distal native coronary artery Unlike the situation in proximal artery segments where both blood flow and pressure gradient across an obstruction are reduced by bypass surgery the distal coronary artery segment is exposed to a new set of dynamic factors including increased flow increased pressure, turbulence and eddy currents Whether normalization of pressure and flow in an artery segment distal to a stenosis accelerates atherogenesis in a susceptible subject is unknown Turbulence and eddy currents may arise from the unnatural time of arrival of pulse waves through the functioning graft as well as from alteration in the contour of the pressure pulse [17] Changes in velocity profile axial flow and rates of shear at the endothelial surface may alter the distribution of intravascular blood elements particularly at this surface Although both pulse wave timing and pressure contours have been described as essentially normal in acute animal preparations [18] the chronic effects of minor alterations in these steady state oscillations are unknown and may predispose to intimal injury and/or thrombogenesis Operative manipulation of the coronary artery may also predispose to intimal injury

Finally the fact that the frequency of a new distal lesion is the same as in unoperated arteries suggests that the findings merely represent the natural progression of atherosclerotic disease The frequency of progression in *distal* segments of operated coronary arteries was the same in vessels which occluded as well as with patent grafts (Fig 11) Although we do not know how long the graft was patent and functioning and whether progression in the distal artery occurred before or after the graft had closed, this finding again suggests that distal progression is a manifestation of the natural disease process

The adverse effects of direct aortocoronary revascularization surgery on the native coronary circulation appear to occur primarily in the early postoperative period and appear to be the result of loss of the proximal segments of grafted arteries—which may have little effect on total coronary blood flow in the distribution of the grafted artery The effect on distal coronary segments is equivalent to the natural atherosclerotic process If the graft life is long proximal progression is a trivial matter Therefore direct revascularization surgery remains a valid therapeutic approach to properly selected patients with coronary artery disease and angina pectoris

Summary

This report relates the postoperative clinical and cineangiographic status of 67 patients select

ed from a total of 202 patients who underwent coronary artery surgery at the Peter Bent Brigham Hospital from July, 1970, to July, 1972 The mean interval after operation was 12 6 months Ninety one per cent of the 67 patients were improved from their preoperative status Forty eight patients (71 per cent) were studied to evaluate recurrence of mild to moderate angina or occurrence of interval myocardial infarction, and 19 patients (29 per cent) were entirely asymptomatic In the 67 patients studied, 112 coronary arteries received a total of 115 grafts (There were 89 ungrafted coronary arteries) Total graft patency rate for the 58 patients in whom angina was totally or significantly relieved was 65 per cent However one or more grafts were patent in 52 (90 per cent) of these 58 patients In grafted arteries progression was found in segments proximal to the graft in 37 per cent of arteries at the site of anastomosis in 10 per cent, and distal to the site of anastomosis in 17 per cent The frequency of obstruction distal to the site of anastomosis was not significantly different from the frequency of progression in nongrafted arteries in contrast to preliminary data from this laboratory Overall and regional progression in grafted arteries appeared to occur primarily within the first four months after surgery and was found thereafter in a constant percentage of vessels studied Progression in coronary arteries was independent of patency or occlusion of the graft to the vessel

It is hypothesized that while proximal progression is probably a consequence of altered hydraulic factors, distal lesions seem to represent natural progression of atherosclerotic disease

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Variant angina pectoris a clinical and coronary arteriographic spectrum

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Since the description of a variant form of angina pectoris by Prinzmetal and associates[1,2] a considerable volume of literature has appeared, primarily in the form of individual case reports which has augmented our knowledge of its clinical features[3-23] The coronary arteriographic findings in this syndrome have been reported by several investigators[7,8,11,23] Although the majority of these reports have concurred with Prinzmetal s hypothesis that variant angina pectoris is associated with severe proximal single coronary artery lesions it has become increasingly evident that such lesions may be minimal or absent Furthermore the role of coronary artery spasm has been brought to the forefront because of both theoretical considerations and direct observations[14,17,21]

Enthusiasm for surgical revascularization has been strong because of the amenability of isolated proximal coronary lesions to bypass graft surgery and the previously reported grave prognosis associated with variant angina pectoris[12]

The purpose of this report is to describe the clinical features and coronary arteriographic findings in eight consecutive patients with variant angina pectoris, emphasizing a diversity of coronary angiographic patterns and a relatively favorable prognosis

Materials and methods

The diagnosis of variant angina pectoris was established in eight patients admitted to the coronary care unit of Parkland Memorial Hospital between March 1971 and April 1974 All patients demonstrated spontaneous episodes of angina like pain at rest accompanied by transient S T segment elevation on the electrocardiogram (ECG) In these patients the S T segment elevation occurred in those ECG leads reflecting either an anterior or an inferior region of ischemia

Myocardial infarction was excluded in each patient by serial enzyme determinations and serial ECG s

Three patients underwent graded exercise testing on an upright bicycle ergometer with continuous Frank lead ECG monitoring Each patient performed three minute periods of exercise at progressively higher work loads until near maximal exercise was achieved or until symptoms or ECG signs of myocardial ischemia supervened None of the patients was taking digitalis at the time of the exercise testing

Cardiac catheterization was performed in all eight patients with coronary cineangiography in seven patients Follow up cardiac catheterization with coronary angiography was accomplished in two patients following surgical revascularization

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Table I Clinical, electrocardiographic, and catheterization data

Patient	*ECG localization during variant angina*	*Exercise test*	*Cardiac catheterization*	*Coronary angiography*	*Hospital course*
MF 52F	Inferior	Negative	LVEDP 3 mm Hg EF 76% normal wall motion	Normal	Temporary pacemaker for CHB asymptomatic on medical therapy
PF 60F	Inferior	Not performed	LVEDP 4 mm Hg EF 92% (post VPC) normal wall motion	Severe 3 vessel disease no collateralization	Asymptomatic on medical therapy
JH 50M	Anterior	Not performed	LVEDP 10 mm Hg EF 59% hypokinetic anterolateral wall	90% stenosis proximal LAD 40% stenosis proximal RCA no collateralization	Asymptomatic following surgical revascularization
JL 36M	Inferior	Not performed	LVEDP 10 mm Hg left ventriculogram not performed	Not performed	Asymptomatic following catheterization
BP 44F	Inferior	Not performed	LVEDP 10 mm Hg bicuspid aortic valve with no gradient left ventriculogram not performed	Normal	Permanent pacemaker for CHB asystolic arrest following catheterization with no angina subsequently
AS 43M	Inferior	Angina S T ↑ Y	LVEDP 6 mm Hg EF 60% hypokinetic inferior wall	100% stenosis proximal RCA distal collaterals present	Asymptomatic on medical therapy
JS 46M	Anterior	Angina S T ↓ Z	LVEDP 17 mm Hg EF 77% normal wall motion	80% stenosis proximal LAD no collateralization	Asymptomatic following surgical revascularization
MN 49F	Inferior	Not performed	LVEDP 9 mm Hg EF 67% normal wall motion	Normal	Asymptomatic on medical therapy

Abbreviations S T S T segment Y superior inferior lead, positive inferiorly Z, anterior posterior lead positive posteriorly ↑ elevation ↓ depression EF ejection fraction LVEDP left ventricular end diastolic pressure LAD left anterior descending coronary artery RCA right coronary artery CHB complete heart block VPB ventricular premature beat

procedures Single plane left ventricular cineangiograms in the right anterior oblique projection were performed in seven patients in order to assess wall motion abnormalities and left ventricular function

Results

Clinical data A summary of the clinical ECG, and catheterization data appears in Table I The patient group consists of four females and four males with ages at the time of diagnosis of variant angina between 36 and 60 years (mean 47) Two patients (AS and JS) described symptoms of classical angina pectoris that preceded the clinical recognition that they had variant angina pectoris One of these (AS) experienced typical angina for two years without a known myocardial infarction, while the other (JS) sustained a subendocardial myocardial infarction and had subsequent exertional angina two months prior to admission for variant angina pectoris

Episodes of chest pain at rest in these patients were of a severe nature often accompanied by diaphoresis nausea and vomiting Sublingual nitroglycerin was effective in producing prompt relief of pain in four of the eight patients in the other four patients nitroglycerin failed to provide relief in a consistent fashion

Electrocardiographic findings All patients demonstrated transient S T segment elevation on a standard ECG obtained during one or more episodes of chest pain The degree of S T segment elevation varied from 1 to 4 mm above the

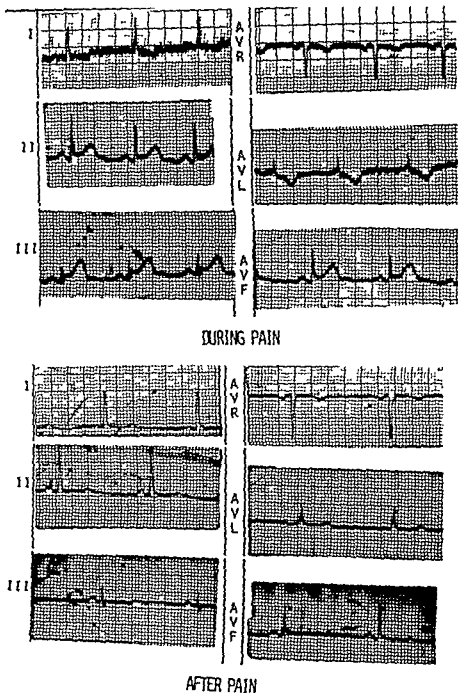


Fig 1 Patient JL. ECG during pain shows S-T segment elevation in the inferior leads (top) After pain had spontaneously subsided, the ECG changes have returned to normal (bottom)

baseline and was generally associated with T waves that were increased in amplitude or had become upright from an inverted pattern (Fig 1) The ECG s following pain reverted to their original patterns except in the case of JH where persistent deep T wave inversions across the precordial leads developed following the onset of variant angina

S T segment elevations were localized to the inferior leads in six patients and to the anterior leads in two patients Ventricular arrhythmias and/or heart block developed in three patients

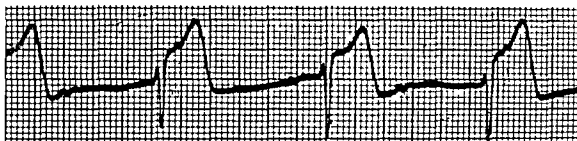


Fig 2 Patient MF ECG during pain displays S T segment elevation and complete heart block with an A V junctional escape rhythm at 53 per minute

during episodes of chest pain Complete heart block with an atrioventricular junctional escape rhythm occurred in patient MF (Fig 2) while patient BP sustained recurrent episodes of complete heart block and ventricular tachycardia Ventricular premature beats occurred during episodes of variant angina in JH, none of the other patients had documented ventricular extrasystoles during the episodes of chest pain

Exercise testing Graded exercise testing was performed in three patients In two patients (AS and JS) the test provoked anginal pain and atypical ischemic ECG changes Patient AS developed 1 mm S T segment elevation in Lead Y of the Frank lead system Patient JS displayed 1 mm S T segment depression in Lead Z which is equivalent to S T segment elevation in Lead V_1 An exercise test resulted in no ECG changes or chest pain in patient MF at a maximal heart rate response of 166 per minute However this test was accomplished several months following her hospitalization for variant angina and she had since developed complete left bundle branch block Five patients did not undergo stress testing because of ECG and symptomatic instability

Cardiac Catheterization Intracardiac pressures were all normal with the exception of an elevated left ventricular end diastolic pressure in patient JS Left ventricular cineangiography in six patients demonstrated normal wall motion in four patients inferior wall hypokinesis in one patient and reduced anterolateral wall motion in one patient Left ventricular ejection fractions were all within the normal range but were lowest in the two patients with localized wall motion abnormalities Ventriculography was not performed in two patients for technical reasons in one and because of a severe anaphylactic reaction to a test dose of contrast medium in another

Coronary arteriography Selective coronary arteriography was accomplished in seven patients Angiographically normal coronary arteries were found in three patients

Patient PF had severe triple vessel disease The left anterior descending artery demonstrated an area of 60 per cent stenosis proximal to its major diagonal branch a 90 per cent stenosis just beyond it, and two discrete areas of 80 per cent stenosis in its most distal aspects The circumflex coronary artery had a 90 per cent proximal stenosis The right coronary artery exhibited diffuse disease including a 95 per cent stenotic lesion of its posterior descending branch No collateral opacification was visualized

The three remaining patients had significant proximal obstruction One (JH) had a 90 per cent stenosis of the left anterior descending vessel just distal to its major diagonal branch and an insignificant (40 per cent) stenosis of the proximal right coronary artery Another (JS) demonstrated an area of 80 per cent stenosis in the proximal left anterior descending artery with otherwise normal vessels (Fig 3) The third patient (AS) had total occlusion of the proximal right coronary artery this patient represented the only instance in which collateral flow was demonstrable

Coronary artery spasm was not observed in any patient in this series however all coronary artery injections were performed following sublingual nitroglycerin administration

Treatment and follow up Six patients were managed nonsurgically and two underwent surgical revascularization procedures Patient JL became asymptomatic and has remained so following a severe anaphylactic reaction during cardiac catheterization Patient BP required insertion of a temporary transvenous pacemaker and later a permanent pacemaker to control episodes of complete heart block and hypotension which accompanied her anginal attacks Immediately following cardiac catheterization she



Fig 3 Patient JS Left coronary artery visualized in the right anterior oblique projection Note the proximal stenosis without other significant disease

sustained an asystolic arrest with failure of the pacemaker to secure ventricular capture Following successful resuscitation generalized deep T wave inversions developed on her ECG but these resolved without enzyme changes She had no further episodes of angina but died suddenly eight months later following an alcoholic debauch Postmortem examination disclosed severe luminal compromise of both the proximal left anterior descending vessel and the proximal right coronary artery by acute hemorrhage into subintimal plaques Coronary angiography had been normal and she was not taking anticoagulant medication Focal myocardial fibrosis was present but there was no evidence of a transmural infarction

Four patients (MF PF MN and AS) received oral propranolol hydrochloride (40 to 80 mg daily) and sublingual isosorbide dinitrate (5 to 10 mg four times a day) This resulted in cessation of all spontaneous anginal episodes In addition patient MF required a temporary transvenous pacemaker to control episodes of complete heart block

Two patients with proximal left anterior descending artery stenosis underwent surgical revascularization An internal mammary artery to left anterior descending anastomosis was performed in patient JH following which there was complete relief of symptoms Repeat coronary angiography two weeks postoperatively revealed a patent anastomosis and left ventricular wall motion had become normal with an associated increase in the ejection fraction from 59 per cent to 77 per cent Patient JS underwent saphenous vein aortocoronary bypass grafting to the left anterior descending coronary artery This was demonstrated to be patent at repeat catheterization nine months postoperatively and he has continued to be free of angina

Currently seven of the eight patients are alive and free of angina The mean follow up period for the entire group has been 17 months

Discussion

Variant angina pectoris differs from angina pectoris of the classic form in two major clinical respects (1) the pain is not exertionally related and (2) the ECG during episodes of pain reveals transient S T segment elevation rather than depression[1,2] While the pathophysiologic basis for classic angina pectoris appears to be well established[2,4] the mechanisms governing variant angina pectoris are less clear It does appear

however, that a sudden reduction in myocardial oxygen supply, i e , coronary artery spasm, may be an important factor since episodes of variant angina occur at times of lowest myocardial oxygen demand Hemodynamic studies by Guazzi and co workers[25] have shown that there are no changes in heart rate or blood pressure preceding the ECG changes of spontaneous variant angina

Mounting evidence has accumulated which implicates transient coronary artery spasm as the cause of some cases of variant angina pectoris either acting alone or in concert with fixed obstructive coronary arterial lesions Experimentally temporary coronary artery interruption in the dog has been shown to produce reversible S T segment elevation within the ischemic portion of the left ventricle [1,2,26,28] Coronary artery spasm in patients with variant angina has been directly observed in the catheterization laboratory by several investigators [7,14,16,17,23] but has been most convincingly documented by Oliva Potts and Pluss [17] The occurrence of entirely normal coronary arteriograms and/or autospy examinations in patients with variant angina pectoris[8,11,13,15,18,20,22] appears to be most simply explained by the spasm hypothesis

The predominant feature of MacAlpin's series of 20 patients with variant angina was significant focal obstructive disease of the major coronary artery predicted from the distribution of S T elevation seen in the ECG during attacks [18]

Four of our patients displayed significant stenotic lesions at angiography The coronary arteriographic patterns were predictable from the ECG changes during pain in three patients All were proximal stenoses compromising the lumen by at least 75 per cent A fourth patient (PF) had significant stenosis of the right coronary artery as expected, but in addition, there were severe stenoses of the left anterior descending and circumflex vessels

Collateral channels were demonstrable in only one patient (AS) supporting the view that a fundamental difference exists between classic angina and variant angina with regard to the mechanism of myocardial ischemia in these two disorders Transient, episodic myocardial ischemia such as might occur from coronary artery spasm would not tend to promote collateral vessel formation, whereas chronic myocardial underperfusion is a well recognized stimulus to collateralization

The absence of coronary arteriographic abnormalities in three patients with S T segment elevation in the inferior leads and transient complete heart block in two of the three is best explained by temporary right coronary artery spasm Pretreatment with sublingual nitroglycerin may have prevented our observing this phenomenon during coronary arteriography although it seems likely that coronary spasm when an etiologic factor, is demonstrable only during episodes of chest pain [17]

The occurrence of S T segment elevation and angina during exercise testing in two patients is of interest Both patients had sustained previous myocardial infarctions Prinzmetal and co workers[1,2] and more recently MacAlpin Kattus and Alvaro[18] have emphasized normal exercise tolerance in patients with variant angina However Cheng and co workers[16] were able to provoke angina and S T segment elevation by exercise testing or rapid atrial pacing in two out of four patients with variant angina and normal coronary angiograms There are several previous reports of exercise induced S T segment elevation occurring in patients with variant angina [3,11,12,15,29]

The possibility that coronary artery spasm contributes to the genesis of variant anginal attacks tends to complicate the therapeutic approach The development and improvement of myocardial revascularization techniques for classic angina pectoris have stimulated enthusiasm for their application to patients with variant angina The major reasons that patients with variant angina have been considered good surgical candidates are (1) the proximal location of their lesions with good distal vessels (2) preserved left ventricular function and (3) the desire to prevent myocardial infarction and sudden death [12]

However a great deal of skepticism has arisen recently concerning a surgical approach in variant angina The finding of coronary spasm involving the distal as well as the proximal aspects of the coronary arteries has suggested that surgical bypass of a proximal fixed obstructive lesion in this setting may not provide relief from the disorder [16,18,22,23] There is as yet not sufficient experience with surgical revascularization in such patients to be more than speculative about its efficacy

Surgery was performed in two patients in this

series with proximal left anterior descending stenosis and good distal vessels in hopes of alleviating pain and preventing infarction or sudden death. Surgery was not considered in the three patients with normal coronary arteriograms, in the patients with severe distal coronary artery disease, or in the patient who did not undergo coronary arteriography. The patient with isolated complete right coronary artery occlusion had generous angiographic collateral filling of the distal right coronary artery from the left coronary system and an excellent response to drug therapy and therefore was not considered a surgical candidate.

The effect of drug therapy in the long term medical management of variant angina pectoris has not been adequately evaluated. Prinzmetal and co workers[1,2] reported that prevention of attacks was afforded following treatment with the vasodilator nylidrin hydrochloride. Experience with currently popular long acting vasodilators in this group of patients is lacking. The effects of propranolol were impressive in five patients treated by Guazzi and co workers.[30] However the mechanism of its action in this situation is unknown. It has been our experience that the frequency of episodes of chest pain was dramatically reduced in the four patients in this series selected for treatment with propranolol and isosorbide dinitrate.

Long term follow up of 10 medically treated patients by MacAlpin, Kattus, and Alvaro[18] has revealed only a single death. Similarly, the prognosis in our eight patients has thus far been good. Apart from a single sudden death, there have been no major intervening ischemic events.

It is concluded that the coronary arteriographic patterns in patients with variant angina pectoris are not always predictable from the ECG changes that appear during pain. While fixed obstructive disease is generally appreciated from angiographic examination, variant angina may occur with no apparent atheromatous disease, with proximal single vessel stenosis, or with diffuse three vessel involvement. Coronary artery spasm is the most attractive hypothesis to explain the entire syndrome at this time, particularly in those patients with normal coronary arteriograms. Selection of the appropriate mode of therapy must be highly individualized from the coronary arteriographic findings and the response to medical therapy. Myocardial revascularization may be of value in properly selected individuals but is probably contraindicated in those patients who demonstrate diffuse coronary artery spasm, and is of course definitely contraindicated in those patients with normal coronary arteriograms. The over all prognosis for those patients assigned to medical management appears to be more favorable than has been previously reported, but continued observation will be required to demonstrate this conclusively.

Summary

The clinical course and coronary arteriographic findings in eight patients with Prinzmetal's variant angina pectoris are reviewed and contrasted to previously reported cases. In six patients with S T elevation inferiorly, three had normal coronary arteriograms, one had complete right coronary artery occlusion, one had diffuse triple vessel disease, and one did not undergo coronary arteriography. In two patients with S T elevation anteriorly, severe stenosis of the anterior descending coronary artery was present. Medical treatment in four patients and surgical revascularization of the anterior descending coronary artery in two patients were both accompanied by marked symptomatic improvement. Spontaneous loss of angina occurred in two patients. During 17 months mean follow up, seven patients have remained free of angina and one died suddenly. Variant angina pectoris may be accompanied by a variety of coronary arteriographic findings and the prognosis appears more favorable than previously reported.

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Permanent pacing in disorders of sinus node function

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The development of permanent pacemakers for the treatment of symptomatic A V block has simplified the management of patients with this type of conduction disturbance [1] However the role of permanent pacing in disorders of sinus node function is not well established.[2,3] Due to symptoms of cerebral dysfunction in patients with sinus arrest severe sinus bradycardia or prolonged sinus pauses after episodes of tachy cardia permanent endocardial pacing has been utilized to maintain a minimum ventricular rate and cerebral perfusion during the asystolic inter vals [4,5] This approach appears to be a logical extension of pacemaker therapy and the low morbidity and mortality of the percutaneous en docardial method suggests application of this form of treatment may be justifiable [1] The same rationale has been used in patients exhibiting digitalis sensitivity who without the pacemaker could not have been given this glycoside for the control of congestive failure or intermittent su praventricular tachycardia [6]

A group of 33 patients exhibiting sinus node disease who were treated with permanent pace makers were evaluated to determine the value of this mode of therapy This revealed a twofold incidence of mortality during the 36 month study period compared to our own experience of paced patients with fixed or intermittent A V block

Methods

All permanent pacemaker applications were reviewed for the interval of August 1969 to August 1972 Inclusion into the study was based on adequate documentation of the symptoms and electrocardiographic abnormality Follow up in formation was obtained from the pacemaker clinic where the usual pacemaker evaluation was obtained[7] in addition to a brief interview which recorded the present clinical state interval ill nesses or complications and medication sched ule In those instances where patients were confined to home or nursing care units personal correspondence with the attending physician was obtained to verify the state of the individual.

For the study patients were divided into two groups Patients with sinus bradycardia or arrest without an escape mechanism formed Group I Those patients with alternating bradycardia and tachycardia formed Group II Group II included three patients who manifested digitalis sen sitivity with extreme slowing of the sinus rate in the intervals between episodes of ectopic atrial rhythms All patients that presented in the pace maker clinic with pacemaker dominated rhythms were further evaluated by inhibition of the unit by externally applied precordial cur rents [8] The underlying rhythm and rate were used in this study evaluation and in some cases used as a guide to further management [9] The en tire group was analyzed for the incidence and the etiology of mortality and morbidity The underly ing electrocardiographic pattern and rhythms were studied to determine factors other than pacemaker function that could have influenced

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Table II Alternating bradycardia tachycardia Group II

Patient	*Sex*	*Age*	*Symptom*	*ECG*	*AT*	*AF*	*AFib*	*Clinical diagnosis and associated disorders*	*Duration (months)*	*P*	*Inn.*	*Fate*
1 RB	F	56	Syncope	SB	–	+	+	Pulmonary emboli	35	P+AF	AF	Alive
2 HF	F	61	Dizziness	SB	+	–	–	None	4	ST	–	Alive
3 GG	F	70	Syncope	SA,SB	–	+	+	CHF	13	P	S	Alive
4 MG	F	65	Dizziness	SB	+	–	+	None	30	S	–	CVA
5 ZH	F	65	Palpitations	SB	–	+	+	None	17	P	AF	Alive
6 JM	F	76	Weakness	SA,SB	+	–	–	Carcinoma prostate	34	P	SB	CA prostate
7 RP	M	59	Syncope	SA	+	–	–	RHD (MS)	35	P	S	Alive (Rec PAT)
8 GP	M	ı1	Chest pain	SA SB	+	–	–	Angina MI	14	P	SB	Alive CHF
9 CQ	F	80	Syncope	SB	–	–	+	None	22	P	SB	Alive
10 LR	F	73	Syncope	SB	–	–	+	Generalized arteriosclerosis	1	–	–	CVA
11 RW	F	76	Dyspnea	SB		+	+	Angina	20	P	AFib+3 HB	CVA
12 IY	F	61	Weakness	SA,SB	–	–	–	Diabetes	6	P	AF	Alive embolus brach
13 GB	F	71	Syncope	SA	+	–	+	Hypertension	6	P	PAT/SA	Alive CVA
14 ZB	F	74	Palpitations	SB	–	+	+	Angina	4	–	–	CHF
15 FC	F	73	Syncope	SB	–	–	+	Angina CVA	4	AFib	–	MI
16 KS	F	ı7	Syncope	SB	+	–	–	Angina	9	PAT/S	–	Alive (mesenteric embolus)

For abbreviations see Table I

Table III Patients with peripheral or cerebral embolus

Patients	*Age*	*Sex*	*Site of embolus*	*ECG*	*Treatment*	*Comment*
1 PH	84	M	Right femoral	S AFib	Embolectomy	
2 ED	83	F	Left femoral	S AFib and LB[3]	Embolectomy	
3 WY	73	M	Cerebral	AFib AF junctional	Cardioversion	Rhythm change and embolus 24 hours after cardioversion
4 MW	74	F	Cerebral	S AFib	–	
5 RV	ı9	F	Right femoral	PAT atrial arrest and junctional	Embolectomy	
6 JB	79	M	Right femoral	3 HB	Embolectomy	Permanent pacer followed
7 CH	83	F	Left brachial cerebral	S AFib	Embolectomy	Anticoagulants
8 PB	47	M	Cerebral	AFib AF S	–	Anticoagulants
9 RG	82	F	Right femoral	S	Embolectomy	
10 IY	62	F	Right brachial	AFib SB SA	Embolectomy	Pacer 5 months prior to embolus

For abbrevi tions, see Tabl I
Patient 12 Table II

tion In Group II there were six deaths of which three deaths were due to massive cerebral infarc tion One patient in each group died of congestive heart failure One noncardiac death occurred in each group Three significant but nonfatal com plications occurred in Group II These events were a brachial embolus requiring surgical re moval a mesenteric embolus treated conserv atively and one cerebrovascular accident of probable embolic etiology

Pacemaker clinic results

Fifteen of the Group I patients were checked in the clinic Fourteen of these were pacing at the preset rate of the pacemaker without competi tion Only one patient showed an intrinsic sinus rate fast enough to completely inhibit the pace maker Following external inhibition of the de mand pacemakers electrocardiograms displayed progression to complete heart block in two pa tients two with atrial fibrillation and slow ven

Table I Sinus bradycardia or arrest Group I

Patient	Sex	Age	Symptom	ECG	*Clinical diagnosis and associated disorders*	*Duration (months)*	*Pacer clinic*		*Fate*
							Spontaneous	*Inhibited*	
1 KB	F	57	Syncope	SB	Angina	4	P	SB	Alive
2 HB	F	63	Syncope	SA	Angina inf MI	14	P	S	MI
3 SD	M	86	Syncope	SB	CHF ASHD	1/3	—	—	CHF
4 FF	M	59	Syncope	SA	Inf MI chronic renal insufficiency	9	P	SB	Alive
5 AF	M	78	Syncope	SA	Angina pectoris	1	P	S	MI
6 CH	F	81	Dyspnea	SB	CHF previous MI	21	P	S/3 HB	Alive
7 JH	F	65	Dizziness	SB	Diabetes, hyper tension	3	P	CHB	Alive
8 GH	F	64	Syncope	SB	Angina hypertension	4	P	SB	Alive
9 GMac	F	73	Dyspnea	SA	Angina	1	—	—	MI
10 CM	F	71	Syncope	SB	Diabetes hyper tension	6	P	SB	Alive
11 EM	F	62	Syncope	SA	None	10	S	—	Alive
12 PM	M	54	Weakness	SB	None	36	P	SB	Alive
13 BM	M	78	Syncope	SA	None	11	P	AFib	Alive
14 GM	M	77	Dizziness	SB	None	5	P	SB	Alive
15 MS	F	78	Syncope	SA	Previous inf MI	8	P	SB	Suicide ?digitalis toxicity
16 LS	M	60	Dizziness	SB	Angina	8	P	SB	Alive
17 EV	F	70	Syncope	SA	None	36	P	AFib	Alive

Abbreviations AF atrial flutter AFib atrial fibrillation AT atrial tachycardia CHF congestive heart failure CVA cerebrovascular accident, 3 HB third degree A V block LB3 left bundle branch block MI myocardial infarction P pacing at the time of evaluation PAT paroxysmal atrial tachy cardia RHD rheumatic heart disease S normal sinus rhythm SA sinus arrest SB sinus bradycardia (50 per minute or less) Spont, spontaneous ST sinus tachycardia and deceased.

the results The details of the group with perma nent pacemakers are summarized in Tables I and II In all patients Medtronic demand pacemak ers* of the unipolar or bipolar type were im planted

In addition to the pacemaker data hospital records for the same period of the study were re viewed for patients whose discharge diagnosis in cluded peripheral or cerebral embolus This information was obtained in an attempt to deter mine if embolic complications were occurring in nonpacemaker patients who would otherwise have gone undetected by review of the pacer clinic data alone Those patients who required embolectomy or suffered a probable cerebral em bolus were reviewed Patients with mitral stenosis, myocardial infarction postcatheteriza tion vascular occlusion or cerebrovascular acci dents of unclear etiology were excluded The elec trocardiograms of these patients were analyzed. These data are summarized in Table III

* Medtronic Inc Minneapolis Minn Model Nos 5944 5945 and 5842

Results

There were 17 patients in Group I and 16 pa tients in Group II, including three patients who manifested extreme slowing of the heart rate when treated with digitalis The age ranged from 56 to 86 years with no difference in the average age of both groups In the brady tachy group (II) the majority of the patients were females (13 out of 16) while Group I was nearly equally divided (10 out of 17 were females)

Syncope was the chief symptom in 11 of the 17 patients in Group I and in eight out of 18 patients in Group II In Group I, eight patients had sinus arrest and nine patients had sinus bradycardia In Group II, 10 patients had sinus bradycardia two patients had sinus arrest and four patients had both sinus bradycardia and sinus arrest.

The average duration of pacing was 19 4 months in Group I and 16 3 months in Group II The averages were reduced by the early mor tality of many of the pacemaker recipients

There were five deaths in Group I Three of these five deaths were due to myocardial infarc

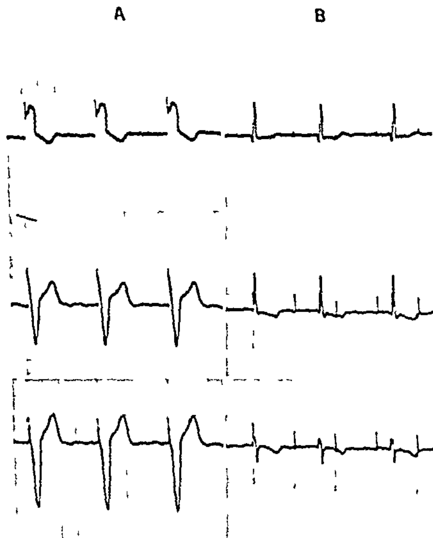


Fig 2 Patient 17 Group I In *A* Leads I II and III show unipolar pacing without competition. In *B* after the pacer is inhibited, atrial fibrillation is noted and was consistently observed on all following visits to the clinic (four visits at three month intervals)

the hospital and seven of the nine patients demonstrated changing supraventricular rhythm disturbances which appeared to be related to the embolic events [3]

Discussion

Sinus node dysfunction may produce varied clinical problems In Group I patients the major concern is sinus slowing or arrest without an escape mechanism and resultant syncope Group II patients also presented with bradycardia transient asystole and syncope but their management is complicated by the unpredictable occurrence of rapid atrial ectopic rhythms The etiology of the syndrome is unclear although coronary artery disease is frequently present in the affected individuals The natural history of this syndrome is also unclear [2] In the absence of a single etiology and a predictable future course it is unlikely that a single form of therapy will be uniformly effective in patients with this syndrome

The use of permanent endocardial pacing in this group of patients has successfully controlled syncope and dizziness which are the primary symptoms Symptoms were controlled as the presence of an adequate ventricular rate was assured by the endocardial pacing site Although

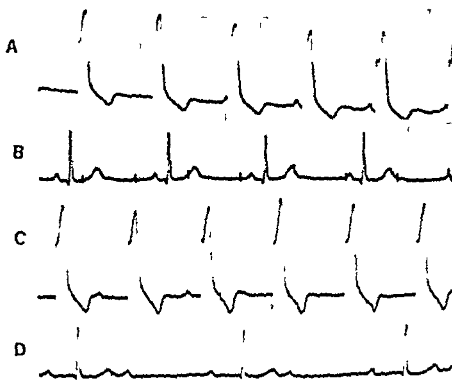


Fig 1 Patient 7 Group I The top strip (A) shows pacing without competition In B the unipolar pacemaker is inhibited, uncovering spontaneous sinus mechanism In C the strip shows pacing similar to the clinic record of three months earlier In D pacer inhibition shows complete A V block with ventriculophasic sinus arrhythmia that has developed in the interval between visits.

tricular rates with the remaining 10 patients in sinus mechanism at variable rates below 60 per minute

In Group II 14 patients were available for study Ten of these patients were pacing without competition Upon inhibition of the pacemaker, three patients demonstrated atrial fibrillation with one of the three patients in complete heart block and the remaining seven patients demonstrating sinus mechanism at varying rates

Changes in rhythm and/or A V conduction were observed in eight of the 24 patients in both the groups who presented with pacemaker dominated rhythm Had no pacemaker inhibition been performed the progression to complete heart block would not have been appreciated in three patients unless pacemaker failure occurred [10] The change of supraventricular mechanism to atrial fibrillation with intact A V conduction in five patients was easily recognized by the analysis of the postpacemaker inhibition electrocardiograms

Seven patients developed atrial fibrillation one to twelve months after pacemaker insertion Five of these patients were followed from four to 16 months Atrial fibrillation was noted on all subsequent clinic visits suggesting that the atrial fibrillation was both chronic and stable Two patients died within a month after developing atrial fibrillation and no conclusion can be reached from the limited duration of the fibrillation nor can a direct relationship be established to relate their deaths to the rhythm disturbance

In order to find out whether intermittent supraventricular tachyarrhythmias could be the underlying cause for systemic embolism of undetermined etiology hospital records of patients admitted with peripheral or cerebral emboli documented during a three year period were analyzed Changing supraventricular mechanisms were seen on serial electrocardiograms in eight out of 10 patients seven of whom showed intermittent atrial fibrillation (Table III) Of the eight patients with arrhythmias, the only patient without atrial fibrillation demonstrated atrial arrest alternating with atrial tachycardia Only two patients failed to manifest atrial ectopic activity while in the hospital Both of these patients had femoral embolectomies and one patient subsequently required a permanent pacemaker for complete heart block In Patient No 10 a brachial embolus occurred five months after the insertion of a pacemaker as a part of the treatment of the alternating bradycardia tachycardia syndrome In patients Nos 1 through 9 of this group embolism was the cause of admission to

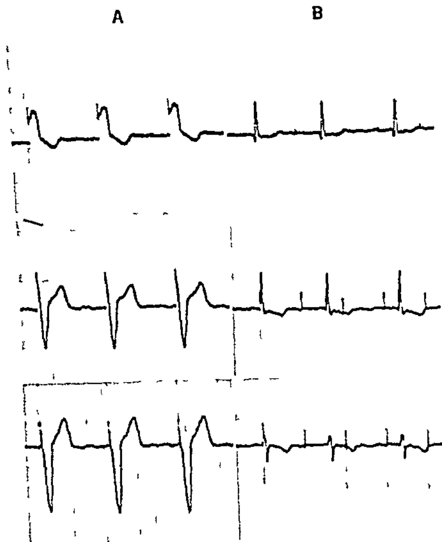


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Sinus node dysfunction may produce varied clinical problems In Group I patients the major concern is sinus slowing or arrest without an escape mechanism and resultant syncope Group II patients also presented with bradycardia transient asystole and syncope but their management is complicated by the unpredictable occurrence of rapid atrial ectopic rhythms The etiology of the syndrome is unclear although coronary artery disease is frequently present in the affected individuals The natural history of this syndrome is also unclear[2] In the absence of a single etiology and a predictable future course it is unlikely that a single form of therapy will be uniformly effective in patients with this syndrome

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other writers have suggested atrial[11] and coronary sinus[12] pacing as the methods of choice these pacing sites have not been widely applied The maintenance of sequential atrioventricular pacing is ideal but not necessary as the syncope is related to total failure of cardiac contractility and not dependent on the small increment in cardiac output produced by atrial augmentation of ventricular diastolic volume Pacing from the atria requires more elaborate pacemaker units[13] may be unstable, and presumes normal A V conduction will persist if initially present[14] Even though bifocal sequential atrioventricular pacing may overcome this problem stable pacemakers of this type are still in the early stages of development and more clinical experience is needed[13] In our experience the syncope has been uniformly controlled with the endocardial pacing site suggesting that elaborate pacing apparatus and more extensive surgical intervention are of theoretical rather than practical importance Analysis of the conduction system via precordial inhibition has documented the subsequent development of A V block in three patients (Fig 1) Had atrial pacing been chosen these patients would have required ventricular endocardial pacing for control Although syncope was controlled in Group II patients the presence of the pacemaker appeared not to affect the pharmacologic control of the tachyarrhythmias which was generally difficult The pacemaker allowed for more liberal use of digitalis glycosides especially in the digitalis sensitive patients[2] Readmission for the treatment of supraventricular tachycardias was common

Apparent cures of the syndrome were present in three of the of Group II individuals who experienced no further attacks of rapid heart action Rhythm analysis with pacer inhibited showed atrial fibrillation with a satisfactory ventricular rate and intact A V conduction Atrial fibrillation occurred in seven of the 29 patients checked in the clinic with complete A V block in one of these * The atrial fibrillation was stable in the five patients who were followed for four to sixteen months and present on each subsequent pacemaker evaluation (Fig 2) The patients with intact A V conduction could have been managed with digitalis alone as the underlying ventricular rate was satisfactory This observation suggests that the induction of atrial fibrillation may effectively terminate the spectrum of sinus node dysfunction[15,16] The spontaneous development of stable atrial fibrillation may also suggest in some cases that the "syndrome of sinus node dysfunction represents an intermediate state between sinus mechanism and chronic atrial fibrillation The possible transient nature of the syndrome is suggested by the five long term survivors who developed atrial fibrillation and spontaneously terminated the clinical syndrome

During the study period 11 of the 33 patients died Deaths in Group I were a result of ischemic heart disease in four patients and probable digitalis toxicity in one patient In Group II massive cerebral infarction was the cause of death in 3 of 6 patients who died The possibility that these cerebrovascular episodes were embolic cannot be excluded Emboli are suggested as a cause of these terminal events by the occurrence of a nonfatal cerebrovascular episode a brachial embolus requiring surgical removal and a mesenteric embolus in the Group II patients Similar embolic complications have been observed by others[3] and suggest that recurrent atrial arrhythmias with spontaneous conversion may be the etiology of peripheral emboli in the absence of acquired or congenital cardiac disease[11] Support for this hypothesis was obtained from the data of patients who were treated for embolic problems in the absence of known predisposing factors (Table III) Analysis of the electrocardiograms of these patients revealed alternating supraventricular rhythm disturbances similar to the patients in Group II The finding of similar embolic complications in the paced and nonpaced patients with intermittent atrial ectopic rhythms suggests that the arrhythmias may be related to the development of emboli in the majority of patients with documented and probable embolic episodes with atrial fibrillation being the most common arrhythmia observed These observations suggest that anticoagulation may prove to be a useful therapeutic adjunct in Group II patients

The causes of death in Group II patients with sinus node dysfunction appear to differ from patients with acquired A V block The majority of deaths in patients with third degree A V block were due to congestive heart failure or myocar

* Two patients died within a month after the onset of atrial fibrillation and further pacer clinic evaluation was not possible One of these two was the patient with complete heart block

dial infarction (30 out of 182 patients or 16 per cent) during the same period of observation [18] Patients in Group I with sinus node dysfunction resemble those with A V block as the deaths were primarily cardiac Only in Group II were cerebral deaths nonfatal cerebrovascular episodes and peripheral emboli noted, suggesting a difference in mortality and morbidity unrelated to the pacemaker and possibly a result of the changing atrial rhythms

The observations made herein suggest that permanent endocardial pacing has a limited role in the treatment of sinus node dysfunction especially in those in Group II Although syncope is successfully managed many aspects of the problem appear unsolved Deaths due to underlying cardiac disease remain unaffected by the pacemaker therapy Control of supraventricular ectopic rhythms remains difficult and readmissions for these are common The advent of stable atrial fibrillation appears curative and may be worthy of controlled induction in certain instances It is possible that in some cases the clinical syndrome of sinus node dysfunction is a transient state prior to development of stable atrial fibrillation The occurrence of fatal and nonfatal embolic complications may suggest anticoagulants be used as prophylaxis in these patients

Pacemaker therapy for sinus arrest or bradycardia associated with syncope has effectively prevented intermittent syncopal attacks The values of pacemaker therapy in patients with alternating bradycardia tachycardia remains uncertain as the majority of the affected individuals continue to manifest ectopic rhythm disturbances and embolic complications

Summary

Thirty three patients with disorders of sinus node function treated with permanent endocardial pacemakers were evaluated. Study of the underlying heart rate and rhythm was accomplished by external inhibition of pacemakers The development of stable atrial fibrillation was documented in 7 out of 29 patients studied and effectively terminated the syndrome of sinus node dysfunction Embolic complications appeared to be an important factor in the morbidity and mortality in patients with changing supraventricular rhythms Pacemaker therapy effectively controlled syncopal episodes due to bradycardia but recurrent episodes of tachycardia and problems associated with this remained unaffected.

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The association of fixed and dynamic left ventricular outflow obstruction

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Fixed obstruction to the left ventricular outflow tract at valvular subvalvular, or supravalvular levels as well as coarctation of the aorta, may be complicated by an additional dynamic obstruction [1-5] This is due to abnormal systolic anterior motion of the mitral leaflet causing additional narrowing of the left ventricular outflow tract [6,7] We have been able to predict preoperatively the presence or absence of complicating dynamic obstruction by echocardiography

Materials and methods

Twelve children ranging in age from six to 18 years were evaluated because of clinical signs of severe aortic valvular or subvalvular stenosis Eleven children were studied by echocardiography, cardiac catheterization and angiocardiography One patient did not undergo catheterization because of a bleeding disorder Patients were studied under basal conditions in the supine position and the effects of pharmacologic agents on the left ventricular outflow tract were not studied

Echocardiographic examination was carried out with a Hoffrel ultrasonoscope Model 101 A 2 25 MHz transducer focused at 5 cm or a 3 5 MHz unfocused transducer was used The echocardiograms were recorded both on Polaroid film and on a strip chart recorder running at 50 or 75 mm per second The transducer was placed in the fourth left interspace within one inch of the left sternal border, and the mitral valve echo identified This was scanned in its full extent through the left ventricular cavity by rotating the transducer from inferolateral to superomedial positions The right and left septal surfaces with left ventricular endocardium were obtained by rotating the transducer laterally from the mitral valve echo Near gain was adjusted until the right septal surface was clearly visualized.[8]

Results

In all children, severe obstruction to the left ventricular outflow tract requiring surgical relief was identified Valvular obstruction was present in seven and four children had a discrete subvalvular membrane The one patient who could not be catheterized had clinical signs of tight valvular aortic stenosis

All patients had symmetrical left ventricular and septal hypertrophy Ten patients had normal anterior mitral valve leaflet motion in systole Two patients had abnormal anterior systolic motion of the anterior mitral valve leaflet (Figs 1, *A* and 2 *A*) One child nine years old had valvular stenosis and one, ten years old had a discrete subvalvular membrane The ratio of the thickness of their left ventricular walls to their septa was 1 1 and 1 1 1, respectively The degree of left ventricular hypertrophy was marked the thicknesses being 1 9 and 1 6 cm respectively

All children underwent open heart surgery Following relief of the fixed obstruction in the 10 cases with normal mitral valve motion a residual gradient of no greater than 20 mm Hg was

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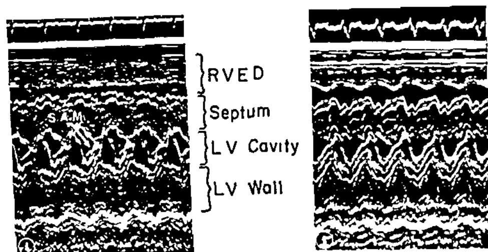


Fig 1 A a 9 year old child with valvular stenosis and abnormal systolic anterior motion of the anterior mitral valve leaflet (arrow) B postoperative echogram shows minimal residual abnormal systolic motion (arrow) The left ventricular outflow tract does not appear as narrow LV left ventricle RVED right ventricular end diastolic dimension and SAM systolic anterior motion

found. This gradient was measured during surgery after the patient had come off cardiopulmonary bypass

One of the patients with systolic anterior motion had an intraoperative gradient of 125 mm Hg across the left ventricular outflow tract after aortic valvotomy A septal myotomy reduced the gradient to 20 mm Hg The other child with systolic anterior motion had a discrete thick fibrous membrane resected from the subvalvular area In addition the left ventricular outflow tract was so narrowed that a septal myotomy was performed. A preoperative gradient of 235 mm Hg was completely abolished by the two procedures.

In both these patients the mitral valve motion returned to normal or near normal in the postoperative period (Figs 1 B and 2 B)

Histologic examination of the resected portions of the septum showed hypertrophy of normally oriented muscle fibers (Fig 3 A) In addition the patient who had the discrete subvalvular membrane showed multiple small areas of fibrosis. A histologic preparation from the septum of a patient with idiopathic hypertrophic subaortic stenosis is shown for comparison (Fig 3 B)

Discussion

There are now at least 29 reported cases of the association of fixed left ventricular outflow tract obstruction with dynamic subvalvular obstruction[1,5] Most authors have suggested that these cases represent the chance occurrence of two separate diseases namely the fixed obstruction and idiopathic hypertrophic subaortic stenosis. In our two patients this appeared unlikely for the following reasons (1) the hypertrophy of the left ventricular wall and septum was symmetrical Asymmetrical septal hypertrophy is an essential finding for the diagnosis of idiopathic hypertrophic subaortic stenosis[8,10]

(2) The histology of the resected portion of ventricular septum showed hypertrophy of normally arranged muscle fibers The disorientation usually seen in asymmetric septal hypertrophy was not present (Figs 3 A and B)

(3) Dynamic obstruction to the left ventricular outflow tract is very rarely reported in association with congenital heart disease other than fixed left ventricular outflow tract obstruction or coarctation of the aorta[11,12] This frequent association with only these forms of congenital heart disease suggests a causal rather than a chance relationship

The echocardiographic finding of abnormal systolic anterior motion of the mitral valve has previously been regarded as diagnostic of the disease entity of asymmetric septal hypertrophy[7,13] However it may be that it is specific only for a mechanism of left ventricular outflow tract obstruction which is related to severe symmetric hypertrophy Asymmetric septal hypertrophy

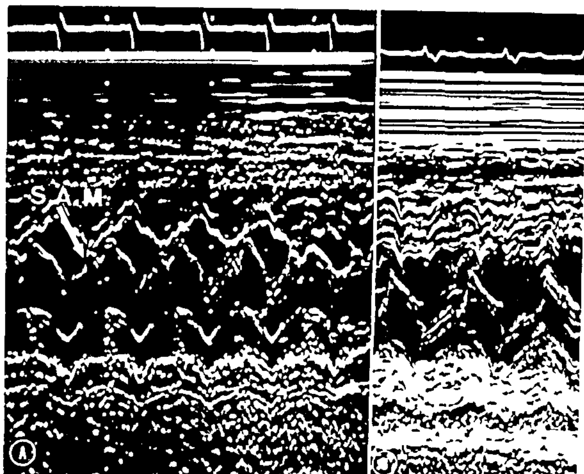


Fig 2 A a 10 year old child with a discrete subvalvular membrane and abnormal systolic anterior motion of the anterior mitral valve leaflet (arrow) B postoperative echogram shows near normal mitral valve motion SAM systolic anterior motion

would also be required before the diagnosis of asymmetrical muscular (dynamic) subvalvular obstruction could be made

It is possible that in some instances the presence of a constant afterload on the left ventricle from birth results in the exuberant concentric hypertrophy seen in these cases The left ventricular outflow tract is therefore narrowed The massive hypertrophy of the papillary muscles and the commonly associated fibrosis of them[14] may then result in their dysfunction leading to abnormal mitral valve leaflet motion with further obstruction to the narrowed left ventricular outflow tract

Relief of fixed obstruction especially to right ventricular outflow has been reported to result in a gradual reduction of the residual gradient [1 16] This however may not occur on the left side and a significant residual gradient with symptoms may persist for years after relief of the fixed obstruction [1 3] This fact has been stated by some authors as an argument toward the co existence of two separate diseases [3 16] namely fixed left ventricular outflow obstruction and idiopathic hypertrophic subaortic stenosis Persistent postoperative dynamic obstruction in the left ventricular outflow tract results in an afterload to the left ventricle which is a continuing stimulus to left ventricular hypertrophy and hence abnormal systolic anterior motion of the mitral valve This then becomes a self perpetuating mechanism

The often marked residual left ventricular outflow tract obstruction may result in death in the immediate postoperative period [1] This possibility and also the persistence of a left ventricular outflow tract gradient with symptoms for many years emphasizes the need to recognize the co existence of dynamic and fixed obstruction preoperatively Our study has demonstrated that echocardiography enables one to accurately predict this In addition the resection of the subaortic portion of the septum results in normalization of the mitral valve echo

Summary

Twelve patients were investigated echocardiographically and angiographically and were

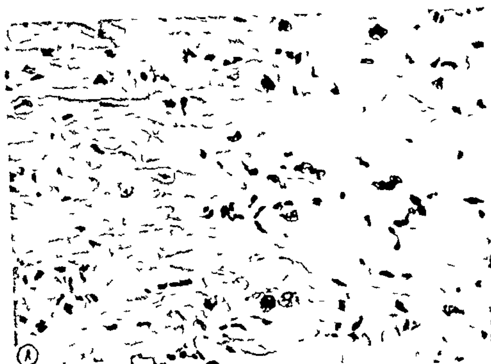


Fig 3 A section from septum of the patient with discrete *subvalvular* membrane and dynamic obstruction. Hypertrophy of normally arranged longitudinally oriented muscle *fibers is shown* No disorientation of myocardial cell processes or of intracellular myofibrils is apparent *Hematoxylin* and eosin ×530

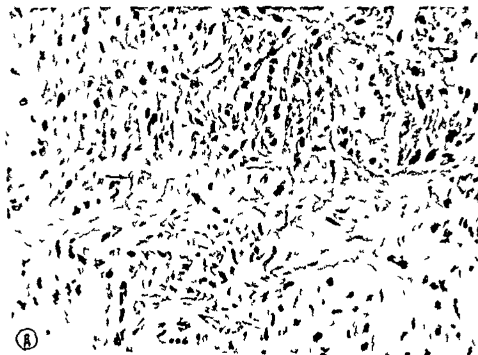


Fig 3 B section from the septum of a patient (not in this series) with classical idiopathic hypertrophic subaortic stenosis with obstruction. The overall architectural disarray and disorientation of intracellular myofibrils (arrows) are both evident *Hematoxylin* and eosin, ×500

shown to have severe fixed obstruction to the left ventricular outflow tract Eight had valvular stenosis and four had discrete subvalvular membranes Two of the patients had additional dynamic obstruction of the left ventricular outflow tract This was recognized preoperatively by echocardiography because of abnormal systolic motion of the mitral leaflet At the time of definitive surgery for relief of the fixed obstruction the additional dynamic obstruction was identified and treated since persistent residual obstruction may lead to death in the immediate postoperative period or to long term symptoms The dynamic left ventricular outflow obstruction is probably a result of the hypertrophy produced by the fixed obstruction

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Effect of clofibrate on progression of coronary disease a prospective angiographic study in man

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Controlling the major risk factors—hyperlipidemia hypertension and cigarette smoking—is considered a principal means of preventing future cardiovascular disease[1-3] Hyperlipidemia may be improved by dietary modification and use of a variety of lipid lowering agents within both primary and secondary prevention studies there is some evidence that these approaches may decrease the incidence of new cardiovascular complications[1,8*]

An essential question still unanswered is whether a cholesterol or triglyceride lowering regimen actually influences the degree of narrowing of the coronary arterial system The purpose of the present study was to investigate this point to assess whether clofibrate (Atromid S) given over a year s period of time is capable of influencing the rate of progression or regression of coronary disease as assessed by coronary angiography This study falls in the secondary prevention category the patients all having proved coronary disease prior to entrance in the study most having been subjected to coronary surgery as well

Methods

Patients selected for this study were those who already had had selective coronary angiography and, in all but two patients coronary artery surgery The surgery included internal mammary artery implantation into the myocardium (Vineberg operation) in six patients—performed in 1968 and saphenous vein aortocoronary bypass graft in 32 patients—performed between the years 1969 and 1972 Two additional individuals volunteered for the study and did not have surgery All patients having these procedures except those previously on clofibrate were offered the opportunity of joining the study without regard to preoperative blood lipid measurements Those who agreed were paired by age and randomly assigned to treatment or placebo groups The trial was doubleblind, one capsule containing either 500 mg of clofibrate or placebo being given four times daily * The patients were provided with manuals and instructions in proper diet depending on lipoprotein type but rigid control of this aspect was not attempted. The drug code was broken only after the entire study was terminated.

Forty patients completed the study 16 in the clofibrate group and 24 from the placebo group The average age was 48 1 years and 49 1 years for these two groups respectively and the mean weight change was −2 kilograms and +0 32 kilograms in the clofibrate and placebo groups The drug groups were not statistically significantly different with reference to either of these variables blood pressure or cigarette smoking (p >0 3 in all)

An additional 25 patients failed to complete the study for a variety of reasons 16 of these having been started on clofibrate and nine on placebo Failure to complete the study was

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Pr mary pre tio ef rs to p t ents ons d ed to be free of kn wn coro ry d se se t th ception of the t dy wh le se ndary pre ent nd tes that the drug o dietary i terv nti n is inst t ted in group having prior evidence of coro ry artery disease

*Ident cal capsule contain ng e the clofibr te or pl cebo w re sup pl ed by the Ay rst Company

Table I Cholesterol and triglyceride values

	Placebo	Clofibrate
Baseline		
Cholesterol (mg %)	252 ± 9	260 ± 8
Triglyceride (mg %)	196 ± 12	183 ± 16
Change		
Cholesterol (%)	+3 0 ± 3 2	−3 3 ± 5 1
Triglyceride (%)	+2 3 ± 5 4	−13 7 ± 7 1*

p = 0 045 the change in lipids compares the baseline value with the average over the ensuing year

Table II Change in coronary arteries in placebo and clofibrate groups

	Placebo group (24 patients)		Clofibrate group (16 patients)		
	Total	Progressed	Total	Progressed	P
Coronary arteries	96	24	64	19	0 26
Bypassed	27	18	20	14	0 40
Nonbypassed	69	6	44	5	0 32
50 99% obstructed	38	17	32	16	0 39
Bypassed	18	14	17	13	0 46
Nonbypassed	20	3	15	3	0 35

prompted by apparent adverse drug reaction in eight patients (seven in the clofibrate group) changing clinical status necessitating repeat coronary angiography earlier than one year (five patients four taking clofibrate and one taking placebo) death (one patient from each group) and patient noncompliance violators (10 patients four from the clofibrate and six from placebo groups) Inspection of the grouping of these patients suggests that the overall results were not significantly biased by failure to complete the study The apparent drug side effects included clofibrate group—four patients with gastrointestinal intolerance, two patients with muscular aching and one patient with general malaise placebo group—the one patient complained of gastrointestinal distress

The patients were seen as outpatients once every three months at which time their clinical course was evaluated compliance of the prescribed drug regimen was ascertained physical examination performed, and fasting plasma lipid values were obtained The patient's reliability in taking the drugs was determined by careful questioning and by using riboflavin tablet markers

Prior to the patients first outpatient visit, they received a letter containing several instructions, including the recommendation to take three 5 mg tablets which were enclosed (riboflavin) for each of two days before the office visit. They were not told what the pills were nor was an explanation of the instruction given to the patient. Urine samples later obtained were examined for fluorescence produced by the drug This method is inferior to placing the riboflavin marker with in the actual capsule but does serve to verify a patient s general ability to follow instructions In all cases the patients claiming to take their medications regularly were also found to have fluorescence within the urine 'Violators, patients discontinuing the placebo or clofibrate were dropped from the study within six months of inception

Serum cholesterol (direct) triglyceride (enzymatic procedure), and lipoprotein electrophoretic pattern (in agarose) were determined[9] prior to surgery (two samples) and at intervals of three months over a year s period of time The blood was collected after a fast of 12 hours Type IV lipoprotein patterns were noted in 20 of the patients 16 of these had triglycerides greater than 200 mg per cent (range 170 to 302 mg per cent) Type IV patterns were considered to be present when there were not fasting circulating chylomicrons the age adjusted triglycerides were elevated, and electrophoresis showed an increased very low density lipoprotein (pre beta) band.[3,9] For purposes of determining change in the lipid measurements, the initial preoperative value was compared with the mean of the three six, nine, and twelve month values This approach was used since it was reasoned that the degree of coronary atherosclerosis was being affected over the entire period by the blood lipids Initial and final arterial blood pressures were determined, averaging both the cuff and intra arterial recording techniques

Selective coronary angiography was performed preoperatively and after one year using the Judkin s technique with 76 per cent Renografin and filming each coronary artery in multiple views right and left anterior obliques and anteroposterior projections The aortocoronary bypass and internal mammary implants were also visualized in the appropriate cases Determination of change in coronary artery pattern was made by one of four independent radiologists

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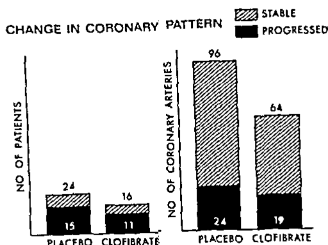


Fig 1 Histogram showing frequency of progression of coronary artery disease in patients taking placebo and clofibrate The number within the black rectangle indicates coronary arteries showing progression the number above the bar refers to the total

and one author all had no knowledge of the patient s drug group Agreement in interpretation was achieved in all instances in four cases a third independent observer was utilized as arbiter For purposes of analysis each patient s coronary artery tree was divided into four parts—the right coronary artery main left left anterior descending and circumflex coronary artery—including each of their respective branches Stability progression or regression of coronary disease was determined in each of these four vessels Progression was judged to be present when greater obstruction or total occlusion of a main artery or one of its branches could be clearly delineated Thus change in coronary disease was evaluated in 160 coronary arteries among the 40 patients completing the study In order to further analyze the data the coronary arteries were also subgrouped as to whether they had or had not received an aortocoronary bypass since bypass grafting seems to influence rate of progression of coronary disease [10] Here the main left coronary artery was considered not to have been bypassed unless both left anterior descending and circumflex vessels had received a saphenous vein implantation [10] Statistical analyses were performed using the two sample proportion test and paired and nonpaired t tests

Results

Lipid measurements (Table I) The initial preoperative serum cholesterol and triglyceride levels of the placebo and clofibrate groups were not significantly different. The mean cholesterol values were elevated to a mean of 252 ± 9 mg per cent (± 1 S E) and 260 ± 8 mg per cent and the mean values for triglycerides were 197 ± 12 and 183 ± 16 mg per cent respectively Twenty patients were found to have Type IV lipoprotein patterns preoperatively seven of these were in the clofibrate group and 13 were control subjects All but one of the patients had a preoperative triglyceride value above 120 mg per cent and 31 of 40 had initial cholesterol levels equal to or greater than 220 mg per cent

The placebo group showed no significant change in the level of cholesterol or triglyceride over the year s period of time (Table I) There was a slight but not statistically significant fall in plasma cholesterol in the clofibrate group averaging −3 3 per cent ($p = 0\ 15$) and a significant decline in the triglyceride level of this group (average −13 7 ± 7 1 per cent $p = 0\ 045$) This change was also statistically significant when the clofibrate group was compared with those taking placebo

Effect on coronary artery disease (Table II Figs 1 and 2) Progressive coronary disease was observed in 15 out of 24 patients (63 per cent) of the placebo group and in 11 out of 16 (69 per cent) patients from the clofibrate group Nineteen out of 64 coronary arteries in the clofibrate group showed progressive narrowing and 24 out of 96 arteries manifested progressive narrowing in the placebo group (Fig 1) The differences between the groups were not statistically signifi

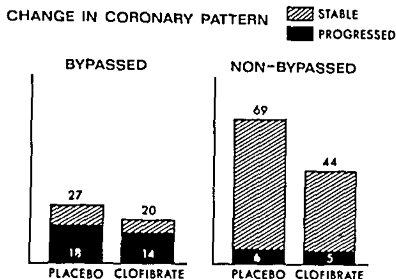


Fig 2 Histogram showing progression of coronary artery disease in placebo and clofibrate groups corrected for those vessels that had and had not been bypassed The number within the black rectangle indicates number of coronary arteries progressing while the number above the bars refers to the total

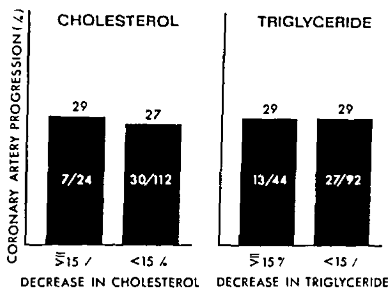


Fig 3 Bar graph showing the percentage of coronary arteries progressing in patients showing a decrease in cholesterol or triglyceride equal to or greater than 15 per cent versus those showing a change in cholesterol and triglyceride of less than 15 per cent The numbers within the bar refer to the number of coronary arteries progressing (numerator) and total coronary arteries (denominator) The number above each bar refers to the resultant per cent progression of coronary artery disease in each of the groups

cantly different Regression in the degree of coronary narrowing was not observed

These data were also considered by dividing the coronary arteries into those which had and those which had not been bypassed (Fig 2) [10] Fourteen out of 20 bypassed vessels from the clofibrate group showed progression, again not statistically significantly different from controls (18 out of 27, p = 0 40) Analyzing only non bypassed coronary arteries 5 out of 44 from the clofibrate group and 6 out of 69 from the placebo group showed progression insignificant (p = 0 32)

Vessels which initially are moderately to severely obstructed seem more prone to develop narrowing than those vessels with only mild obstruction [10] In view of this, coronary arteries which had obstruction of 50 to 99 per cent preoperatively were considered separately again correcting for those which were bypassed and nonbypassed—no significant difference between groups in the rate of progression of coronary disease was noted (p = 0 46 and 0 35) (Table II)

The change in coronary pattern was further analyzed with regard to cholesterol and triglyceride levels recorded during the year of study

Table III Effect of average cholesterol and triglyceride levels on progression of coronary disease

Cholesterol levels	*Number*	*Progressed*	*Stable*	*Triglyceride levels*	*Number*	*Progressed*	*Stable*
All arteries							
< 225 mg %	48	14	34	< 140 mg %	48	9	39
226 275 mg %	60	11	49	141 200 mg %	56	20	36
> 275 mg %	52	20	32	> 200 mg %	52	13	39
Bypassed arteries							
< 225 mg %	12	10	2	< 140 mg %	11	4	7
226 275 mg %	17	8	9	141 200 mg %	22	7	15
> 275 mg %	18	13	5	> 200 mg %	13	5	8
Nonbypassed arteries							
< 225 mg %	36	4	32	< 140 mg %	37	2	35
226 275 mg %	43	3	40	141 200 mg %	34	5	29
> 275 mg %	34	7	27	> 200 mg %	39	5	34

Lipid measurements were incomplete in 1 patient, accounting for the discrepant totals in the cholesterol and triglyceride groupings. No biologically significant relationship between lipid level and coronary progression is shown (see text). Number refers to arteries.

Table IV Relationship of fall in serum cholesterol and triglyceride to progressive coronary disease*

	Fall in cholesterol ≧ *15%*		*Cholesterol change* < *15%*		
	Total	*Progressed*	*Total*	*Progressed*	P
Patients	6	4	28	19	0 48
Arteries	24	7	112	30	0 40
Bypassed	9	6	30	23	0 46
Nonbypassed	15	1	82	7	0 37

	Fall in triglyceride ≧ *15%*		*Triglyceride change* < *15%*		
	Total	*Progressed*	*Total*	*Progressed*	P
Patients	11	8	23	17	0 47
Arteries	44	13	92	27	0 49
Bypassed	11	9	27	22	0 39
Nonbypassed	33	4	65	[illegible]	0 24

*Six patients did not have duplicate baseline lipid measurements and were excluded from the analysis.

since it was reasoned that a drug effect on coronary anatomy may very likely be mediated through its lipid reducing mechanism (Tables III and IV Fig 3) The following subclasses were therefore compared without regard to drug grouping (1) patients with a fall in plasma cholesterol of 15 per cent or greater were contrasted with those not demonstrating a decline of this magnitude (Fig 3) (2) this was repeated with the triglycerides as the variable (3) patients with a mean cholesterol below 225 mg per cent during the year were contrasted with those averaging 225 to 275 mg per cent and those with a mean cholesterol above 275 mg per cent and (4) subjects with a plasma triglyceride of 140 mg per cent or below were contrasted with the subgroup of 141 to 200 mg per cent and those with a triglyceride level above 200 mg per cent In all cases no significant difference in rate of progression of coronary disease was noted (Tables III and IV) Although the incidence of progression was greater at mean cholesterol levels above 275 mg per cent compared with the intermediate cholesterol range (225 to 275 mg per cent) (p < 0 01) no significant difference was evinced between groups showing a mean cholesterol less than 225

mg per cent compared with those *greater than* 275 mg per cent (p = 0 17) Hence the statistical differences appear to have little biological significance

The data were also analyzed considering only those patients initially showing Type IV hyperlipoproteinemic patterns Within this subgroup (admittedly small) clofibrate seemed to exert no significant influence on the frequency of progression of coronary artery disease when compared with the patients taking placebo Thus it was found that six out of seven Type IV patients taking clofibrate had progressive coronary artery disease, whereas nine out of 13 patients in the placebo group with Type IV patterns manifested progressive coronary narrowing Correcting for presence of hypertension or cigarette smoking did not influence the results of the drug therapy

Discussion

Several lines of experimental epidemiologic and clinical evidence both in animals and man support the assumption that hyperlipidemia is related to the development of coronary heart disease [1-4] In the Framingham study [4] serum cholesterol was shown to be the most useful lipid in predicting risk of coronary heart disease Plasma triglycerides have been less firmly linked to the atherosclerotic process and there is controversy concerning the importance of triglyceride as an independent contributor to the risk of developing atherosclerosis [7,11,12] The high prevalence of coronary disease in patients with Type IV hyperlipoproteinemia however makes it likely that this lipid is also instrumental in the development of coronary disease [2]

Controlled studies dealing with primary prevention of coronary heart disease performed in Helsinki, New York and Los Angeles have reported a significantly lower incidence of new coronary events in patients utilizing diets with low saturated fat and cholesterol content when compared with control subjects eating their usual foods two of the studies have reported decreased coronary mortality as well [1,5] Several secondary prevention studies in which lipid modification was investigated in groups of patients with prior overt coronary heart disease, have also indicated that lipid lowering regimens may eventuate in a reduction in the fatal and nonfatal myocardial infarction rates [6,8,13,14]

Clofibrate (ethyl alpha chlorophenoxy isobutyrate CPIB, Atromid S) represents one of the more potent lipid reducing drugs Although its mechanism of action remains complex, it is clear that its most marked effect is on the very low density lipoproteins which are predominantly composed of triglyceride The drug is therefore useful for treating hyperlipoproteinemias of Types IIb III, IV, and V [3]

Overview of results

In order to place the current study in proper perspective several aspects inherent in it should be pointed out (1) the duration of drug use was relatively short (2) coronary angiography provides a rather crude estimate of change in coronary pathology, (3) a relatively small number of patients were evaluated (4) in general the patients studied had fairly extensive degrees of coronary disease, (5) all but two of them had coronary surgery (6) additional dietary modifications were not imposed in a controlled or rigid way, and (7) several of the patients did not have elevated triglycerides and therefore, constitute a group which would be less prone to be benefited by clofibrate It is therefore readily acknowledged that under different conditions the results of the study might not have been the same Notwithstanding these limitations it should be pointed out that the clofibrate group did manifest a significant fall in plasma triglycerides and that there was a substantial progression of lesions in both groups of patients Thus the absence of a significant difference between the placebo and clofibrate groups in the degree of coronary disease progression is probably a valid and important observation The groups remained indistinguishable even when allowances were made for bypassed versus nonbypassed vessels degree of initial coronary obstruction lipoprotein type and level or degree of fall in cholesterol and triglyceride

The results are not surprising in view of the extensive degree of coronary atherosclerosis usually found in patients with overt ischemic heart disease Reduction in plasma cholesterol has been shown to decrease the size of atheromatous plaques in nonprimate experimental animals [15,16] and more recently has been demonstrated to do so in the Rhesus monkey[17] lowering plasma triglycerides has not been studied in this context however Early lipid rich lesions appear

to be the most reversible and it remains in doubt whether accumulation of cholesterol and other lipids within coronary atheromatous plaques in man can be inhibited or reversed, or whether the fibrotic calcific pultaceous components of these plaques[18] can be influenced. Of note in this regard is the observation that regression of coronary artery disease demonstrated by coronary angiography is seldom reported[10] and was not evident in the present study Although recanalization of a coronary thrombus has been described,[19] this would appear to be a rare phenomenon on the basis of our and others data Even ileal bypass surgery one of the more effective ways of reducing plasma lipids is not proved to influence rate of progression of coronary disease.[20]

Clofibrate effect on cardiovascular mortality and morbidity Other studies have revealed that the use of clofibrate may decrease future nonfatal myocardial infarction rate and coronary mortality[6-8,14] Although the design and analysis of these reports have recently been criticized,[21] findings that clofibrate exerts a favorable influence on complications of coronary disease *independent* of significant lowering of plasma lipids[6,8,17] suggests that another mechanism might be operative perhaps the effect of this drug on platelet aggregating tendency Since clofibrate was used for only one year in the study since it was given in patients with advanced coronary disease and since its effect might encompass areas apart from reducing blood lipids the overall value of this agent in preventing future cardiovascular complications cannot be definitively ascertained at this time Nonetheless our study was unable to demonstrate an influence of clofibrate on rate of progression of coronary disease Until positive data are forthcoming we therefore do not recommend use of this drug in patients with advanced atheromatous conditions unless triglycerides remain elevated.

Summary

Lowering blood lipids has been invoked as a means of controlling future coronary events In this prospective study the effect of a lipid reducing agent clofibrate (2 gm daily) on extent of coronary artery disease was investigated Forty patients 32 having aortocoronary bypass six having Vineberg operations two having neither were placed double blind in placebo (24 patients) and clofibrate (16 patients) groups and restudied by selective coronary angiography one year later An additional 24 patients dropped from the study due to adverse drug reactions in eight Each patient s right left anterior descending and circumflex coronary arteries (with their branches) were separately rated according to degree of obstruction The clofibrate group showed a significantly greater fall in triglyceride than did the placebo group (−13 7 per cent versus +2 3 per cent p = 0 45) In the clofibrate group 19 out of 64 coronary arteries (29 6 per cent) showed progressive coronary narrowing not significantly different from the placebo group (24 out of 96 coronary arteries narrowed 25 per cent p = 0 26) No significant differences between drug groups emerged when the data were corrected for degree of fall of blood lipids, initial lipoprotein type or effect in bypassed versus nonbypassed vessels (p always >0 2) Regression of coronary artery disease was not seen We conclude that clofibrate did not significantly influence the rate of progression of coronary artery disease in a one year period.

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Experimental and laboratory reports

Effect of ventricular aberrancy on fibrillation threshold

Myung S Yoon M D
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Excitability is not uniform in ventricular muscle during its relative refractory period because different segments of the myocardium recover from their refractoriness at disparate times. Such non uniformity of excitability has been well recognized as a necessary factor in the induction of turbulent impulse propagation i e fibrillation [1-4] A number of agencies which predispose the ventricle to fibrillation have been shown to increase temporal dispersion of recovery and to decrease ventricular fibrillation threshold [2-4] It has been suggested that aberrantly conducted ventricular beats might be associated with increased temporal dispersion of recovery and increased ventricular vulnerability to fibrillation [5] whereas the normally conducted beats have more uniform recovery of excitability and lower ventricular vulnerability [6] To date however there has been no experimental evidence in support of this assumption

The present study was undertaken to examine the effect of ventricular aberrancy on ventricular fibrillation threshold. The results indicate that rhythmically occurring ventricular aberrant beats per se are not associated with decreased ventricular fibrillation threshold

Methods

The experiments were performed on mongrel dogs weighing 10 to 15 kilograms and anesthetized by intravenous injection of sodium pentobarbital in a dose of 35 mg per kilogram Under artificial respiration the thorax was opened in the midline and the heart was exposed and suspended in the opened pericardium The sino atrial node was crushed and the heart was driven at a constant rate by electrical stimuli applied to the right atrium or one of the ventricles. A femoral artery was cannulated to obtain arterial samples for the determination of blood gas and to record the arterial pressure Arterial blood gas and pH were frequently checked and were corrected if needed. Right bundle branch block (RBBB) was produced by cutting the bundle with the tip of a 14 gauge spinal needle inserted into the right ventricular cavity through the anterior free wall

The bipolar stimulating and recording electrodes were small steel hooks with an interelectrode distance of about 3 mm For atrial pacing a pair of stimulating electrodes were attached to the anterior surface of the right atrium For right or left ventricular pacing the stimulating electrodes were attached to each ventricle at the anterior epicardial surface In order to obtain local electrograms of the right and left ventricles (RV and LV) the recording electrodes were attached to each ventricle at a distance of 10 to 15 mm from the stimulating electrode A combined right and left ventricular electrogram (R LV) was obtained from each one of the pairs of right and left ventricular recording electrodes A Lead II electrocardiogram local electrograms from RV and LV the combined R LV electrogram and the artifact of stimuli (S) delivered to the ventricular stimulating electrodes were all monitored and recorded on an Electronics for Medicine recorder at a paper speed of 50 mm per second The ventricular stimuli were also displayed on an oscilloscope and calibrated by means of a Tektronix current probe amplifier

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after surgically induced RBBB in 12 dogs Fig 1 illustrates the results obtained from one of these experiments The top trace in each panel of the figure is the Lead II electrocardiogram the next two traces the records from RV and LV the fourth trace the combined record (R LV) from each one of the pairs of right and left ventricular recording electrodes and the bottom trace the artifacts of stimuli (S) applied to the ventricles. In panels *A* and *B* during the right atrial (RA) pacing and normal ventricular conduction activity at the RV recording site preceded that at the LV recording site and the combined R LV recording was arranged to show an upright polarity The fibrillation threshold determined in the right ventricle (RVFT) following the normally conducted beat was 24 ma in part *A* and that determined in the left (LVFT) was 32 ma. in part *B* In panels *C* and *D* after RBBB was surgically induced QRS complexes were widened in Lead II the RV activity followed the LV and the reversed order of activation was manifested by the inverted polarity in the R LV record. The RVFT determined following the aberrant beats of the RBBB type was 25 ma in part *C* and the LVFT was 29 ma in part *D* and these values are similar to those obtained before the induction of RBBB

Fig 2 shows the mean values of VFT s determined in all 12 experiments The mean RVFT was 21 2 ± 1 8 ma during normal ventricular conduction and 21 3 ± 2 6 ma following the surgically induced RBBB The mean LVFT was 23 ± 2 7 ma during normal ventricular conduction and 25 0 ± 2 8 ma after the induction of RBBB The difference in the mean VFT s before and after the surgically induced RBBB was not statistically significant It should be noted that the mean LVFT s were slightly higher than the mean RVFT s but the difference was not statistically significant (P > 0 05)

Idioventricular beats VFT s were determined in the right and left ventricles during ventricular aberration produced by pacing of the ipsilateral or contralateral ventricle in the same 12 dogs When VFT s were determined in the same ventricle as that to which the pacing stimuli were applied, both pacing and test stimuli were delivered through the same electrodes Fig 3 depicts the results of one of these experiments In panels *A* and *B* during the RV pacing the RV electrogram preceded the LV with an upright

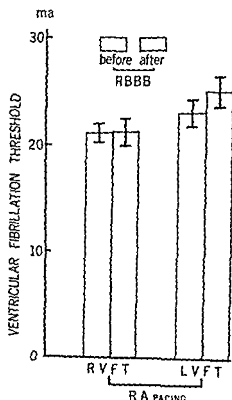


Fig 2 RVFT s and LVFT's obtained from 12 dogs before and after the induction of PBBB The values are expressed as means ± SE. See text for detailed description.

polarity of the combined R LV recording In *A* the RVFT determined by test stimuli applied to the same site as pacing stimuli in the RV was low at 11 ma In *B* the LVFT determined by test stimuli applied to the LV during the RV pacing was 35 ma In panels *C* and *D* during the LV pacing the LV electrogram preceded the RV with inverted polarity in the R LV recording In *C* the RVFT determined by test stimuli applied to the RV during the LV pacing was 31 ma In *D* the LVFT determined by test stimuli applied at the same site as pacing stimuli in the LV was low at 13 ma

Fig 4 shows the mean values of VFT s determined during ventricular pacing in all 12 experiments The mean RVFT determined at the same site as the application of pacing stimuli in the RV was 12 4 ± 1 2 ma and the mean LVFT determined during the RV pacing was 20 1 ± 2 1 ma The mean LVFT determined at the same site as the application of pacing stimuli in the LV was 13 6 ± 1 6 ma and the mean RVFT determined during the LV pacing was 22 9 ± 3 1 ma The results show that the mean VFT s were signifi

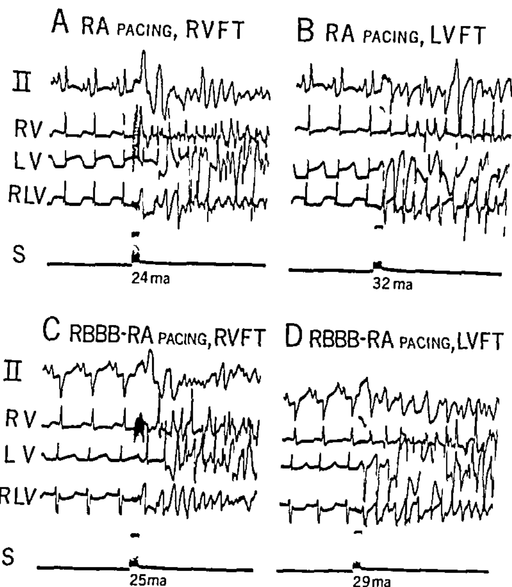


Fig 1 RVFT s and LVFT s determined before (*A* and *B*) and after (*C* and *D*) the induction of RBBB The cycle length of RA pacing was 400 msec *II* indicates Lead II electrocardiogram *RV* and *LV* right and left ventricular electrograms *R LV* the combined electrogram recorded from each one of RV and LV electrodes and *S* the shock artifact of stimuli applied to the ventricular stimulating electrodes See text for detailed description

The patterns of pacing and test stimuli delivered to the heart were programmed by using a variable interval generator and a series of Tektronix waveform and pulse generators The output of the pulse generator triggered a Grass stimulator which delivered pulses of 3 msec duration to the ventricular stimulating electrodes Ventricular fibrillation threshold (VFT) was determined by delivering a train of rapid rectangular pulses across the vulnerable period. The heart was paced by basic stimuli delivered to the right atrium or one of the ventricles at a cycle length of 400 msec, and the train of rapid pulses was delivered to the ventricle after every twelfth basic response The rapid pulses were 3 msec in duration and occurred at 10 msec intervals (100 per second) The train was started at about 80 to 100 msec after the basic response and its duration did not extend the absolute refractory period of the first premature response evoked by the train The intensity of the rapid pulses was gradually increased until fibrillation resulted The VFT was then defined as the minimum current in milliamperes which induced fibrillation Defibrillation was accomplished by direct current (DC) countershock and 10 to 15 minutes were allowed for recovery before the subsequent test was made

Results

Right bundle branch block VFT s were determined in the right and left ventricle before and

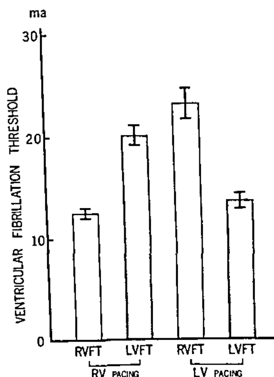


Fig 4 RVFT s and LVFT s obtained from 12 dogs during RV pacing and LV pacing The values are expressed as means ± SE. See text for detailed description

bly the basis for our negative results

Wegria Moe and Wiggers[5] also showed earlier that the VFT did not decrease following aberrantly conducted beats In their study aberrant beats were induced by stimuli applied to a pair of stimulating electrodes and VFT s were determined with test stimuli delivered through another pair of electrodes at some distance from the stimulating electrodes. Their observation and the present study therefore indicate that ventricular vulnerability to fibrillation is not increased in the presence of rhythmically occurring aberrant beats However it is well recognized that ventricular premature beats which are also aberrantly conducted beats are associated with increased vulnerability to fibrillation[3] This indicates that the prematurity is a more important determinant of ventricular vulnerability than is the aberrancy The risk of fibrillation is particularly high when the premature beats are closely coupled and fall in the vulnerable period. The ventricle is vulnerable at this phase since the tissue is irregularly excitable as a result of non uniform rates of recovery at various segments An impulse generated during the vulnerable period, finding some segments responsive and others refractory will be forced to propagate along a tortuous and irregular wave front and this will predispose the ventricle to re entry and fibrillation[14]

The most predictable observation in the present study was that VFT s were significantly lower when they were determined by test stimuli delivered to the same electrodes as the pacing stimuli These results confirm an earlier observation of Han Garcia de Jalon and Moe[3] that the VFT was found to be lowest when the test stimulus was applied either through the same electrodes as the pacing stimuli or in the immediate vicinity of the pacing electrodes When an impulse is initiated at a point in the ventricular myocardium, the initial propagation of the impulse through muscle tissue is relatively slow and may not be uniform in all directions Some asynchrony of recovery must, therefore be expected in the immediately surrounding tissue and this asynchrony should extend through the volume of tissue which is activated through muscle conduction The degree of nonuniformity of recovery as tested by determination of refractory periods was indeed found to be increased within the zone of initial muscle conduction and the fibrillation threshold was accordingly lower near the site of application of pacing stimuli[3] These observations suggest that early premature beats are more likely to induce ventricular fibrillation when they originate at or near the site to which pacing stimuli are applied in the ventricle

Summary

VFT s were determined in 12 open chest dogs at epicardial sites in the right and left ventricles (RV and LV) following normally or aberrantly conducted beats The normal beats were produced by right atrial pacing and the aberrant beats by surgical RBBB or ventricular pacing at an RV or LV site The mean VFT following normal beats was 21 2 ± 1 8 ma in RV and 23 0 ± 2 7 ma in LV The mean VFT following aberrant beats of RBBB was 21 3 ± 2 6 ma in RV and 25 0 ± 2 8 ma in LV The difference between the mean VFT of normal beats and that of aberrant beats was not statistically significant The mean values of VFT s determined in RV or LV following aberrant beats produced by pacing of the contralateral ventricle were not significantly different from those of the normal beats The mean

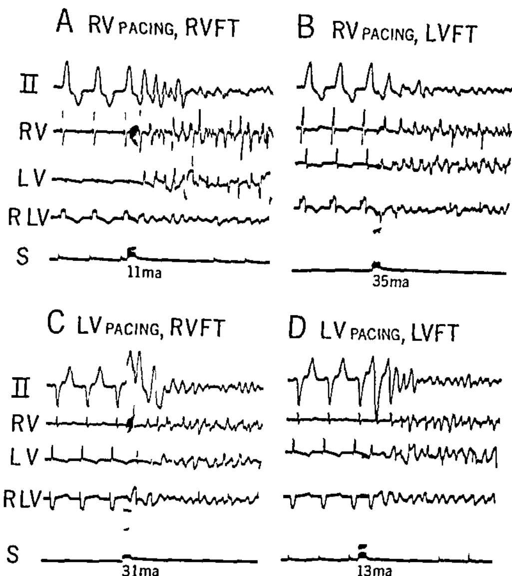


Fig 3 RVFT's and LVFT s determined during RV pacing (*A* and *B*) and during LV pacing (*C* and *D*) The pacing cycle length was 400 msec Other conventions are as in Fig 1 See text for detailed description

cantly lower in both ventricles when they were determined at the same site as the application of pacing stimuli (P < 0 02) However the mean VFT s determined during ventricular aberration induced by pacing the contralateral ventricle were not significantly different from the mean VFT's determined during normal ventricular conduction and after the induction of RBBB (see Fig 2)

Discussion

Complete heart block is associated with idio ventricular rhythm and an aberrant QRS com plex when the level of block is below the bifurca tion of the His bundle This type of heart block may result from coronary artery disease and degenerative lesions involving the intraventricu lar conduction system [7,9] Furthermore ventricu lar pacing is instituted in many of these patients and the resultant ventricular beats are aberrant If the aberrancy of ventricular beats per se in creases ventricular vulnerability to fibrillation as is suggested by some observers [5,6] then the possi bility of ventricular fibrillation could be accor dingly greater in these patients In the present study VFT s were determined in dog ventricles before and during ventricular aberration pro duced by surgical RBBB or pacing of the con tralateral ventricle The results showed that the ventricular aberrancy did not decrease VFT s in these experiments Ventricular fibrillation threshold has been shown to decrease when tem poral dispersion of recovery is increased among adjacent areas of the myocardium [2,3] Ventricular aberrancy would alter the recovery time of one area in reference to remote areas without affect ing the temporal dispersion of closely neighbor ing areas of the myocardium This was presuma

Transcutaneous determination of aortic blood-flow velocities in man

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While physiologic studies have indicated that information about aortic blood flow dynamics may be of considerable usefulness in assessment of heart performance the lack of a widely useful technique has impaired clinical evaluation of this potential.[1,2] At the present time such information is available by angiographic methods whereby left ventricular dimensions are determined chamber volume estimated and outflow rate derived as the rate of change of volume [3,4] Alternate methods which provide direct measurement of aortic flow events by means of catheter tip flow or velocity sensors are under active development [5,6] However both of these techniques require arterial catheterization and this represents a major restriction on their usefulness Thus there remains an important need for noninvasive methods of aortic flow or velocity determination which are applicable to situations where the more expensive troublesome and dangerous invasive techniques are not suitable Such situations include for example continuous monitoring of the postoperative or other high risk patient screening of large numbers of people and measurements in the presence of cardiovascular perturbations such as exercise

As noted by other investigators there is an intriguing possibility of determining aortic blood flow velocities transcutaneously by ultrasonic Doppler techniques Potentially an ultrasonic beam originating from a transducer in the suprasternal notch could be directed toward either the ascending aorta or the aortic arch providing quantitative blood velocity estimates for each of these locations While the assessment of volume blood flow would require the determination of additional parameters notably aortic diameter just the determination of velocities could be of significance clinically

One instrument which allows such noninvasive measurements the pulsed ultrasonic Doppler flowmeter has undergone extensive development [7] Recent clinical trials with this device have clearly demonstrated that flow velocity information can be reliably obtained transcutaneously and used to advantage in cardiac diagnosis [8] While offering considerable measurement capability and versatility the pulsed Doppler instrument is a complex and expensive device which requires skill and training for proper utilization On the other hand, it has been suggested that the anatomy and physiology of blood flow in the thorax may be uniquely suited to a simplified approach using continuous wave ultrasound [9-12] Thus it may be possible to develop a device expressly for the purpose of measuring aortic blood flow velocities transcutaneously which is less versatile than the pulsed instrument but much less expensive and easier to use The present research has been undertaken to evaluate the feasibility of such an approach

Approach

The ultrasonic Doppler technique for determining blood flow velocities has been extensively evaluated.[13,14] Sound waves emanating continu

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VFT was 22 9 ± 3 1 ma in RV and 20 1 ± 2 1 ma in LV These results indicate that the aberrancy of ventricular beats per se is not associated with decreased VFT or increased ventricular vulnerability to fibrillation The most predictable observation was that the mean VFT s were significantly lower in both ventricles when they were determined at the site of application of pacing stimuli The mean values were 12 4 ± 1 2 ma in RV and 13 6 ± 1 6 ma in LV This decrease in VFT may be due to slow conduction and increased asynchrony of recovery of excitability at or near the site of application of pacing stimuli

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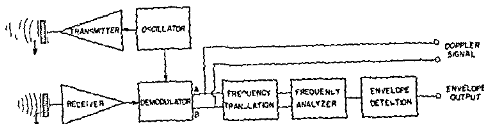


Fig 2 Block diagram of the principal components of the continuous wave ultrasonic Doppler instrument used to measure aortic blood flow velocities See text for further explanation

assessed as a fraction of their control values

In addition to the great potential usefulness of transcutaneous measurement of aortic blood flow velocities it should be noted that there are some potentially important limitations of the technique For example the technique inherently measures velocity not volume flow measures peak velocity which has an unknown relationship to average velocity because the velocity profile is unknown and, for the arch measures velocity in a section of the aorta which carries an unknown fraction of cardiac output Furthermore the need to identify the maximum frequency components of the Doppler signal on a real time basis poses some difficult instrumentation problems the solution of which may impose restrictions on the technique The severity of such limitations can be judged, however only after the validity of the general approach has been demonstrated

Methods

All of the results reported in this study have been obtained with a continuous wave ultrasonic Doppler instrument developed expressly for transcutaneous aortic blood flow velocity measurements The organization and principle components of the device are shown schematically in Fig 2 An oscillator generates a continuous wave at a frequency of 2 5 MHz This signal is amplified and used to drive the transmitting piezo electric crystal which radiates sound waves into the tissue at maximum power densities of less than 25 milliwatts per square centimeter The much weaker reflected wave is amplified and demodulated to yield the Doppler signal At the 2 5 MHz sound wave frequency assuming an angle of incidence close to zero each 1 KHz of Doppler signal frequency corresponds to approximately 30 cm per second velocity of the erythrocytes Therefore for the velocities found in the cardiovascular system the Doppler frequencies are well within the audio range and can be listened to directly

The Doppler signal is then conditioned, translated upward in frequency and processed by a frequency analyzer circuit The maximum excursions of this circuit are indicated by an envelope detector yielding a time trace of the maximum Doppler shift frequencies

Although ultrasonic transducers can be fabricated in a wide variety of configurations depending on the particular application the results presented here were obtained with a transducer consisting of two piezo electric crystals each a semicircular disk mounted edge-to-edge with a two degree angle between them Each crystal is backed by a thin layer of air in order to increase the efficiency of forward radiation

The instrumentation techniques available for continuous wave ultrasonic Doppler technique up to the point of demodulation are well known and established methods have been followed in our device [14] Following demodulation however our approach is new differing markedly from that of others It will be described more completely elsewhere Because the processing technique is new however the Doppler signal which results from demodulation has been taken as the standard data not the envelope signal Thus for all experiments the Doppler signal was recorded on magnetic tape for subsequent processing by a spectrum analyzer (Kay Sonograph) if the output from the frequency analysis circuitry proved to be open to question For each different class of experiment such off line spectrum analysis was performed and the results compared to the tracings obtained from the instrument to verify that the maximum frequencies were adequately indicated

Results

The geometric relationship between a sound beam originating in the suprasternal notch and

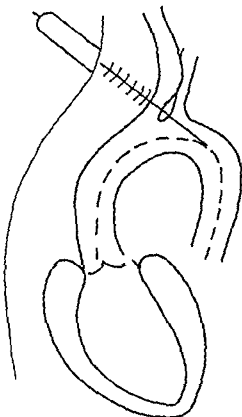


Fig 1 In principle ultrasonic energy radiated from a transducer placed in the suprasternal notch can be directed toward the back of the aortic arch so as to intersect the aortic axis with a shallow angle

ously from a transmitting piezo electric crystal are partially reflected by the moving erythrocytes resulting in a Doppler frequency shift f_D which is determined by the equation

$$f_D = \frac{2 f_0 V \cos \Theta}{C}$$

where f_0 = frequency of transmitted wave C = velocity of sound in tissue (approximately 1 570 M per second) θ = angle between the transducer axis and the blood flow velocity vector and V = velocity of the erythrocytes which are responsible for scattering part of the ultrasonic energy back to the receiving crystal The reflected wave is detected by a receiving crystal and the resulting signal processed electronically to obtain f_D

The difficulty with applying this simple approach to blood velocity measurement in the thorax, as illustrated in Fig 1 is that there are potentially many different portions of vasculature illuminated by the ultrasonic beam Therefore the Doppler signal will be a composite of information about erythrocytes moving with many different velocities at a variety of angles There are, however, two premises regarding illumination of the aorta from the suprasternal notch which suggest that it may be possible to uniquely identify and quantitate blood velocities in the aortic arch

The first premise is that a sound beam originating from the suprasternal notch can be directed so as to be nearly parallel to the central axis of the aorta somewhere near the top of the aortic arch Thus the angle between the sound beam and the velocity vector of the blood in this section of the aorta will approach zero and the cosine of this angle will approach unity

The second premise is that the velocities in the aortic arch are sufficiently high that the V cos θ product for sound waves reflected from this region is larger than for any other portion of the thoracic vasculature—at least during systole Thus, the blood flowing in the arch will be responsible for the highest Doppler shift frequencies

There are some important implications of these premises if they can be shown to be true First since the ultrasonic Doppler technique yields quantitative information about the velocity of the blood in the direction of the beam the presence of a shallow angle between the velocity and the sound beam means that the Doppler data from this region of the aorta can be interpreted quantitatively without any unknown scale factors Second that portion of the vasculature which has the highest apparent velocity in the direction of the beam will be responsible for the highest Doppler shift frequencies in the return signal Therefore, if the maximum Doppler shift frequencies can be separated from the rest of the Doppler signal they will yield a quantitative measure of the blood velocity in a specific section of the aorta

There is the additional possibility that useful velocity signals may be available from the ascending aorta However anatomic variations in the orientation of the aortic root indicate that a near tangential approach of the sound beam to the flow velocity may not be assumed In fact the angle of incidence may actually change during a cardiac cycle If on the other hand, the aortic velocities are high enough and the angle of incidence shallow enough that the maximum Doppler shift frequencies are associated with the information of interest then the data will be of considerable usefulness though not quantifiable in absolute terms Thus, for a subject experiencing cardiovascular changes, alterations of ascending aortic velocity characteristics could be

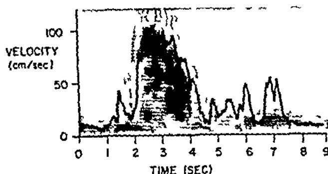


Fig 5 One cardiac cycle of Doppler information processed by off line spectrum analyzer (Kay Sonograph) and on line envelope detector (solid line)

imum Doppler shift frequencies as a function of time Sample tracings from one of the individuals for which this comparison was carried out are shown in Fig 4 The close similarity between the pulsed and the CW data was consistently found and the differences appear to be within the range of normally occurring short term variations and experimental error This result indicates that the maximum frequencies in the CW Doppler spectrum may be validly attributed to that portion of the aortic arch where the ultrasonic beam is nearly tangent to the blood velocity vector

An initial evaluation of transcutaneous aortic velocity measurements in humans was carried out by attempting arch and ascending aorta measurements in 20 apparently normal subjects. All data were obtained with the subjects resting quietly in the supine position Acceptable records were obtained from the arch for all but two of the subjects and from the ascending aorta for all but one subject The spectrum analyzer and envelope records for a single cardiac cycle in one subject are shown superimposed in Fig 5 The ability of the instrument to provide an indication of the frequency envelope is clearly demonstrated. In general the velocity obtained from the envelope detector was in the range of 90 to 100 per cent of the value obtained from off line analysis, and any discrepancy was consistent for a given subject Typical tracings obtained for the ascending aorta and the arch from one subject are illustrated in Fig 6 The presence of a lower peak velocity in the ascending aorta than in the arch was observed in most subjects (never was the arch lower) suggesting that the angle between the sound beam and the velocity is often significantly different from zero for the ascending aorta case

Preliminary comparison of the Doppler velocity signal with volume flow rate was carried out by

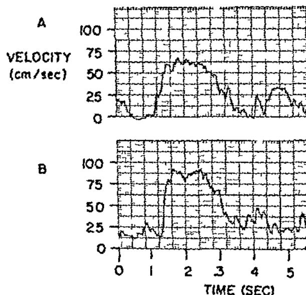


Fig 6 Sample blood flow velocity traces obtained from the ascending aorta, A, and the aortic arch, B of one individual

making transcutaneous velocity determinations on two baboons which had electromagnetic flow sensors chronically implanted on the root of the aorta Several weeks after surgery the animals were lightly sedated with ketamine 5 mg per kilogram intramuscularly and confined in a sitting position with a special chair which allowed the measurements to be made by hand holding the ultrasonic transducer in the suprasternal notch Apparently because lung or some other tissue which greatly attenuates sound waves intervened, useful velocity signals were not available from the arch Adequate signals were obtained from the ascending aorta however and these were recorded, along with the signal from the electromagnetic flowmeter for later comparison Because the angle of the sound beam relative to the flow velocity is not known and

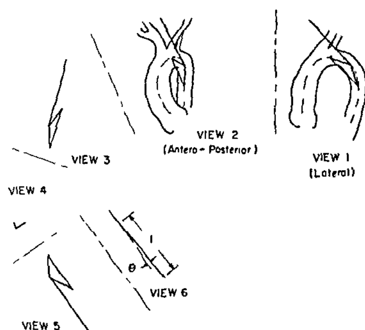


Fig 3 Geometric construction technique by which information contained in the antero posterior and lateral x ray films was manipulated to obtain l the distance from transducer to aortic axis intersection and θ the angle of intersection The transducer placed in the suprasternal notch appeared in the x ray films thereby defining the position of one end of the line

Table I Data for seven individuals for whom the minimum angle (θ) intersection of sound beam and aortic axis was determined by x ray techniques l is the distance from the suprasternal notch to the point of minimum angle intersection

Patient	θ	l (cm.)
1	6 5	7 5
2	8 0	7 7
3	0 0	8 9
4	11 0	8 7
5	4 0	8 4
6	9 5	6 6
7	5 0	9 8
Mean value	6 3	8 2
Standard deviation	3 7	1 1

the aortic arch has been investigated in seven subjects with apparently normal anatomy and cardiovascular function With the transducer probe in place simultaneous radiographs of the anterior posterior view and the lateral view were taken As shown in Fig 3, these orthographic views allow construction of a triangle identifying the plane of the aortic arch The transducer which also appeared in the x ray film provided one end point on a line between the suprasternal notch and the point where the ultrasonic beam is



Fig 4 Maximum frequency envelopes taken from the spectrum analyzer records for several examples of blood velocity in the arch measured by pulsed Doppler (solid lines) and continuous wave Doppler (dotted lines)

most nearly tangent with the aortic axis For simplicity the second point was defined as that point in the lateral view film where a line through the suprasternal notch was tangent with the aortic center line Although not identical with the point which minimizes the angle between the ultrasonic beam and the aortic axis this lateral view tangent point does provide a close approximation and the true minimum angle will be no greater than the angle measured by this technique The data for all seven individuals is summarized in Table I It is noteworthy that even with the tendency of the technique to overestimate the minimum angle the angles are quite small and the assumption that cosine θ equals unity introduces an error of less than 2 per cent

To evaluate the assumption that the greatest Doppler shifts are due to blood flowing in that portion of the aortic arch where the sound beam makes a nearly tangent approach to the velocity vector a comparison of continuous wave and pulsed ultrasonic Doppler techniques was carried out The pulsed Doppler instrument uses a narrow well defined beam and range gating to define a small sample volume from which Doppler information is obtained.[7] To carry out the comparison the pulsed Doppler beam was first directed toward the aortic arch and beam direction and range were varied to the location where the maximum apparent velocities in the aortic arch were obtained Doppler signals from this region of the arch were then recorded Next the continuous (CW) device with its broader beam and lack of range gating was applied to the same individual with approximately the same beam direction and recordings made of the Doppler signals obtained In both cases the Doppler signals were processed with a Kay Sonograph spectrum analyzer and tracings were made of the max

normal subjects suggests that this may not be a major difficulty

These findings indicate that it should be possible to develop an instrument to quantitatively measure aortic blood flow velocities in man which is acceptable for clinical use Furthermore it appears that such an instrument may well be relatively simple inexpensive and easy to use The prototype device used in this study meets most of these objectives However, even greater ease of use could be obtained with a more diverging sound beam which would allow detection of arch velocities without precise aiming of the transducer The feasibility of this modification has been demonstrated by the trial use of a beam with a 28 divergence There are however two difficulties which have hindered this change First the diverging beams with congruent transmitting and receiving patterns from the two crystals are very difficult to fabricate in a compact form. Second, the diverging beam places stringent requirements on the electronics of the instrument Since the sound energy is transmitted over a wide angle and received from a wide angle the energy received from the region of interest is small A very good signal to-noise ratio is therefore required in order to extract acceptable velocity information

While it is important to be clear about the fact that the transcutaneous ultrasonic technique gives information about blood velocity not volume flow rate the clinical usefulness of this method is not likely to rest on the establishment of a known quantitative relationship of the measured velocity to volume flow rate For many potential uses of this technique the magnitude of such flow characteristics as peak flow acceleration and stroke volume is of less importance than information about their rate and direction of change from some control state If the Doppler velocity data can be shown to vary in the same way as corresponding flow variables determination of relative changes will be possible without auxiliary measurements The data comparing maximum velocity and volume flow in the ascending aorta of the baboon suggest that it may be possible to demonstrate such a correlation

Based on these highly encouraging preliminary results, a systematic evaluation of the technique is being undertaken First the transcutaneous accessibility of aortic velocity information together with the convenience and reliability of the method will be determined for wide variations of subject anatomy and disease state Second the degree to which Doppler velocity characteristics correlate with corresponding flow characteristics will be evaluated by performing comparisons with measurements made by standard techniques such as angiography cardiac output determinations and possibly catheter tip flow meters Finally the clinical usefulness of the information provided by the technique will be weighed against the effort and expense involved in making the measurement.

If this proves successful the availability of a convenient method for obtaining aortic velocity information transcutaneously could be of profound importance in several areas of clinical cardiology Perhaps the most immediate application would be to patient monitoring where the detection of short term changes is of primary importance The potential low cost of the instrument and its suitability for use by paramedical staff should make it particularly attractive for this type of application. For diagnostic purposes the method may have particular usefulness under such circumstances as stress testing where invasive techniques are generally unsuitable Ultimately there may be potential for achieving an indication of the heart's mechanical activity which is as simple to obtain and widely useful as the electrocardiogram is for the heart s electrical activity

Summary

A transcutaneous ultrasonic Doppler technique for measurement of aortic blood flow velocities has been developed and compared to more established techniques in order to evaluate its potential usefulness It is possible by this method to quantitate blood velocity in both the ascending aorta and the aortic arch with ease and reliability Ultrasonic access to the aorta from the suprasternal notch proved adequate in more than 90 per cent of the normal subjects examined If further clinical trials prove as encouraging this technique may be of significant value for patient monitoring and cardiac diagnosis

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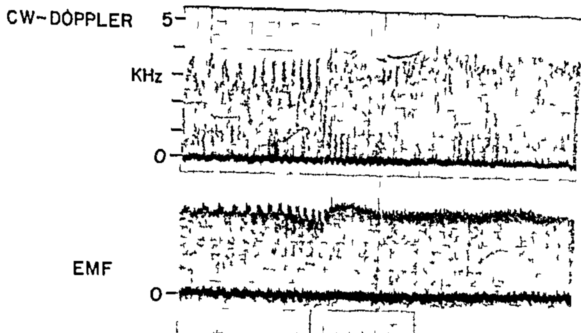


Fig 7 Time course of the response of the ascending aorta volume blood flow (EMF) and velocity (CW Doppler) in the baboon to norepinephrine infusion The EMF signal was uncalibrated since only relative changes were of interest

Table II Ratio of changes of Doppler velocity characteristics to corresponding electromagnetic flow meter changes following inotropic interventions Each is expressed as per cent of control

	Doppler/EMF (X ± S E M)		
Intervention	Peak velocity	Peak acceleration	Area (stroke volume)
Isoproterenol (4 mg /min intravenously) n=12	1 04 ± 0 03	0 84 ± 0 10	1 37 ± 0 06
Metho Hexital (5 mg /Kg intravenously) n= 3	1 01	1 00	1 08

probably not zero (the baboon has a very short ascending aorta) quantitative comparisons of volume flow rate and maximum instantaneous velocity were not possible Rather the time course of the flow and velocity traces were compared qualitatively and the response of each signal to positive and negative inotropic interventions was evaluated These interventions consisted of isoproterenol infusions (4 mg per minute intravenously) administered twelve times in two animals and methohexitol given three times in the two animals The changes of velocity and flow caused by these drugs expressed as a percentage of control valves are summarized in Table II The time course of one animal s response to isoproterenol is illustrated in Fig 7 The deviations from proportionality for changes of acceleration and stroke volume occur primarily because of the lack of a clearly defined envelope during the low velocity periods though it may also be true that the velocity profile changes, becoming more blunt, under conditions of increased inotropism Minor modifications of the instrumentation subsequent to these experiments have indicated that the correlation of isoproterenol induced changes of flow and velocity may be substantially better than that indicated by these preliminary results

Discussion

The results of these experiments indicate that it is possible to measure aortic blood flow velocities and accelerations in man by transcutaneous ultrasonic Doppler methods The basic premises underlying the technique have been validated by the x ray data demonstrating a shallow angle of incidence of sound beam and aortic axis and by the continuous wave pulsed Doppler comparison demonstrating that aortic flow causes the highest Doppler shift frequencies While it is important to remember that ultrasonic access to the aortic arch is required in addition to suitable geometry the successful use of the technique in 18 of 20

normal subjects suggests that this may not be a major difficulty

These findings indicate that it should be possible to develop an instrument to quantitatively measure aortic blood flow velocities in man which is acceptable for clinical use Furthermore it appears that such an instrument may well be relatively simple inexpensive and easy to use The prototype device used in this study meets most of these objectives However even greater ease of use could be obtained with a more diverging sound beam which would allow detection of arch velocities without precise aiming of the transducer The feasibility of this modification has been demonstrated by the trial use of a beam with a 28 divergence There are however two difficulties which have hindered this change First the diverging beams with congruent transmitting and receiving patterns from the two crystals are very difficult to fabricate in a compact form. Second, the diverging beam places stringent requirements on the electronics of the instrument. Since the sound energy is transmitted over a wide angle and received from a wide angle the energy received from the region of interest is small. A very good signal to-noise ratio is therefore required in order to extract acceptable velocity information

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Effects of dipyridamole and acetylsalicylic acid on platelet functions in patients with aortic ball-valve prostheses

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Arterial thromboembolic complications frequently occur in patients with heart ball valve prostheses.[1-4] The thrombi characteristically form on the valve itself[1,5,6] and resulting emboli are often localized in cerebral arteries,[1,4,7] representing a major threat to the patients.

Since the thrombi develop in the arterial system, the platelets play an important role in their formation.[8] Traditional anticoagulant therapy can therefore not be expected to totally prevent systemic thromboembolism, and embolic episodes occur in spite of strict anticoagulation,[1,5,9] although the frequency is considerably reduced.[2,7] This focuses the interest on substances known to modify the function of blood platelets.[10]

The purpose of this investigation was to study the effects of ingested dipyridamole and acetylsalicylic acid (ASA) on platelet function in patients with prosthetic ball valves.

Material and methods

Five male patients with Starr-Edwards aortic ball valve prostheses, implanted one to four years previously, were selected for the study. They were between 49 and 58 years of age and all received digitoxin and warfarin therapy. Cerebral embolic episodes had occurred in two of them; one (AH) was fully restituted, while the other (PO) suffered from slight residual pareses. This patient had a valve of the older series 1200 with a Silastic ball and cloth covered cage; in the others valves of series 2300 with a hollow Stellite ball and cloth covered cage were used.

The two drugs were administered for three separate periods of 21 days with intermissions of at least two weeks, and all patients received the drugs in the same dosage and sequence. First, dipyridamole was ingested in a daily dose of 150 + 75 + 150 mg. Second, 1 Gm. of ASA was taken twice a day, and third, a combination of 150 + 75 mg. of dipyridamole and 0.5 + 0.5 Gm. of ASA was used.

The bleeding time was measured from two incisions by Borchgrevink and Waaler's[11] modification of Ivy's method. Platelets were counted in a hemacytometer by a modification of Nygaard's method,[12] and platelet adhesiveness was determined in native blood according to the modified glass bead filter method of Hellem.[13] Platelet aggregation was estimated with the turbidimetric method described by Born,[14] using the Unigalvo EEL titrator (Evans Electroselenium Ltd., Essex, England). Platelet rich plasma (PRP) for the test was obtained by centrifugation of citrated blood at 300 × g for 15 minutes. Aggregation was initiated with collagen, ADP, and adrenalin in final concentrations of 2.1 μg per milliliter, 0.7 μM, and 3.64 μM, respectively. The response was estimated from the maximal rate of collagen- and ADP-induced aggregation and calculated as the per cent of the mean value in normal subjects at the actual platelet count (Dale and Stormorken, to be published). Whether adrenalin induced the secondary irreversible phase of aggregation was evaluated from the shape of the curves. Platelet survival was determined according to Abrahamsen's[15] method by preparing autologous platelets which were labeled with $^{51}CrO_4^{--}$ and reinjected

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Table I Lactate dehydrogenase (LDH), hematocrit, bleeding time, platelet count, and platelet adhesiveness in patients with aortic ball valve prostheses before drug ingestion The normal range (mean ± 2 S D) is given

Patient	*LDH (U/L)*	*Hematocrit (per cent)*	*Bleeding time (min.)*	*Platelet (no)*	*Adhesive platelets (per cent)*
HF	198	41	7 5	219 000	28
PO	238	48	6 5	214 000	79
AH	432	42	12	256 000	40
KJ	1 050	41	11	200 000	19
JL	1 665	35	13	226 000	5
Mean	716	41 4	10 8	223 000	34 2
Normal range	80 160	40 54	3 11	150 000 350 000	50 100

Table II Maximal rate of platelet aggregation in per cent of normal (collagen and ADP) and appearance of secondary phase of aggregation (adrenalin), platelet half life, and platelet consumption in patients with prosthetic aortic ball valves before drug ingestion

Patients	*Platelet aggregation induced by*			*Platelet half life (days)*	*Platelet consumption (pl /µl/day)*
	Collagen (per cent)	*ADP (per cent)*	*Adrenalin (sec phase)*		
HF	57	81	+	3 5	31 200
PO	106	91	+	3 6	29 700
AH	70	85	+	3 0	42 700
KJ	125	76	+	3 4	29 400
JL	84	76	+	4 1	27 600
Mean	88 4	81 8		3 52	32 160
Normal response	60 140	60 140	+	3 77	30 660

Mean values estimated from Foss Abrahamsen s studies [15]

intravenously Blood samples were collected daily for eight days and the radioactivity was counted. The platelet half life was estimated and the con sumption calculated in platelets per microliter blood per 24 hours [15] For estimation of the degree of intravascular hemolysis, serum lactate dehydrogenase activity (LDH) was determined as described earlier [16]

The assays were performed four times in each patient, before administration of the drugs and during the three periods of treatment In each period the tests were done when the drugs had been ingested for 11 days except the survival studies which started after two weeks

Student s t test for paired comparisons was used for statistical analysis

Drugs Dipyridamole "Persantin' was ob tained from Boehringer Ingelheim West Ger many, and acetylsalicylic acid "Colfarit' was ob tained from Bayer Leverkusen, West Germany

Results

The degree of hemolysis differed widely be tween the five patients with aortic ball valves as judged from their lactic dehydrogenase (LDH) levels (Table I) the upper normal value being 160 U per liter The patient with the most pro nounced red cell breakdown (JL) was anemic in spite of earlier blood transfusions and iron therapy Before drug ingestion the bleeding time was in the upper normal range in the three pa tients with the highest serum LDH The platelet adhesiveness was considerably reduced in four patients as compared to a mean normal retention of 75 per cent (S D = 12 8 per cent) [13] most markedly in the two patients with the strongest hemolysis (Table I) The studies on platelet ag gregation revealed no obvious abnormalities before treatment (Table II) The expected half life of platelets in normal subjects at the same age would be 3 77 days as calculated from

Table III LDH bleeding time platelet number and platelet adhesiveness before and after 11 days of treatment with dipyridamole acetylsalicylic acid (ASA) and both drugs combined

Treatment	LDH (U/L) mean	Bleeding time (min.)		Platelet number		Adhesive platelets (per cent) mean
		Mean	S.D	Mean	S.D	
Before drugs	716	10 8	2 85	223 000	21 000	34.2
Dipyridamole	728	9 7	2 97	215 800	46 100	35 2
ASA	729	>20		231 300	28 600	32 8
Combined	745	>20		238 700	32 600	33 0

Table IV Effects of dipyridamole and ASA on platelet aggregation The maximal rate of aggregation induced by collagen and ADP is calculated in per cent of normal and the number of patients showing secondary aggregation by adrenalin is listed.

Treatment	Maximal rate of aggregation (per cent)				Secondary aggregation by adrenalin, (No of patients)
	Collagen		ADP		
	Mean	S D	Mean	S D	
Before drugs	88 4	27 3	81 8	6 4	5
Dipyridamole	79 0	16 2	88 0	9 9	5
ASA	21 0	14 2	89 4	10 3	0
Combined	15 4	16 9	70 4	23 6	0

Abrahamsen s results [15] Compared to this the mean platelet half life in our patients was slightly shorter 3 52 days but neither this difference nor the slight increase in platelet consumption was statistically significant in this small material.

Ingestion of dipyridamole in daily doses of 375 mg did not cause significant changes in any of the parameters of platelet function (Tables III IV and V) The mean platelet half life rose to 3 72 days but this was entirely due to the prolongation from 3 0 to 4 2 days in one patient (AH) as was the moderate reduction in mean platelet consumption

After administration of 2 Gm of ASA daily the platelet aggregation was considerably changed. The aggregating response to collagen particles was markedly reduced in all subjects with a lowering of the mean value from 88 4 to 21 0 per cent of normal (Table IV) The difference is statistically highly significant (p <0 001) The secondary phase of aggregation induced by adrenalin disappeared in all subjects after ASA The concentration of ADP used was too low to induce secondary aggregation at any time during the study and the response observed reflects the first phase of aggregation which remained unaltered by the medication ASA prolonged the bleeding time considerably in all patients to 12 5 minutes in one subject (PO) and to more than 20 minutes in the others As mentioned, they all received anticoagulant therapy throughout the study

Table V Effects of dipyridamole and ASA on platelet survival and platelet consumption in patients with aortic ball valve prostheses

Treatment	Platelet half life (days)		Platelet consumption (pl./µl/day)	
	Mean	S D	Mean	S D
Before drugs	3 52	0 40	32 160	6 050
Dipyridamole	3 72	0 37	28 840	5 730
ASA	3 72	0 41	31 370	4 000
Combined	4 00	0 91	30 720	5 670

In the third period of medication with a combination of the two drugs in lower doses the effects observed were essentially the same as after ASA alone (Tables III IV and V) The mean platelet half life increased from 3 72 after ASA to 4 0 days which was again attributable to

the change in one patient (PO), and none of the differences observed between the four series was significant (Table IV) The bleeding time and platelet aggregation were influenced to the same marked extent by the combined treatment as by 2 Gm of ASA alone

The degree of hemolysis as reflected by the LDH values [17] was not affected by the drugs (Table III)

Discussion

The mechanisms behind the disturbed platelet function in patients with prosthetic ball valves as reflected by decreased adhesiveness and shortened platelet life span[6,18] or increased consumption [19] are probably complex The intravascular hemolysis regularly found in such patients[20] might be of importance since ADP is liberated from red cells Even if ADP is rapidly removed from plasma [21,22] the concentrations near the valve may be high enough to cause aggregation of platelets an early step in the formation of arterial thrombi and also to induce platelet refractoriness toward ADP [23,24] Adhesive platelets might be consumed by thrombus formation and the increased platelet consumption could be caused by direct damage of the platelets by the impact of the ball [25] Finally the effects on the platelets may be due to a combination of these mechanisms A more extensive discussion on platelet function in patients with aortic ball valves is given elsewhere [26]

Arterial thrombi are characteristically composed of aggregated platelets and fibrin strands [8,27] Adhesion of platelets to subendothelial structures and platelet aggregation are early steps in thrombus formation [28,29] ADP probably plays an important role in the thrombotic mechanism it is responsible for platelet adhesion to foreign surfaces [12] it induces primary platelet aggregation [30] and in higher concentrations it induces the release reaction whereby large amounts of ADP are liberated causing massive irreversible platelet aggregation [31] Inhibition of release is associated with diminished aggregation by collagen and impaired secondary aggregation by ADP and adrenalin [10,32,34] Experimental data further indicate the role of ADP in thrombosis Thus, application of ADP outside the wall of venules[35] and intravenous injection[36,37] provoked formation of platelet thrombi Consequently, ADP liberated from red cells during continuous intravascular hemolysis may, at least in part be responsible for the strong tendency to arterial thromboembolism in patients with prosthetic valves In addition, the disturbance of blood flow by the valve will favor deposition of platelet aggregates on the foreign surface represented by the valve itself or endothelial tissue exposed by the operation

Although coagulation is triggered by platelet release and aggregation [8] the primary participation of platelets in arterial thrombosis explains the relative insufficiency of oral anticoagulation and theoretically this type of thrombosis could better be prevented by substances that modify platelet function Dipyridamole added to PRP is a rather weak inhibitor of aggregation initiated by collagen[10,34] and ADP [34,38] and of serotonin release induced by collagen and adrenalin [10] These in vitro effects on aggregation have not been found to appear after intravenous administration of the drug in rabbits [39] Harker and Slichter[19] found no effect on platelet aggregation or bleeding time of 400 mg of dipyridamole ingested daily in their patients with prosthetic heart ball valves but, surprisingly, the considerably shortened platelet survival times were completely normalized In the present study, no effects of dipyridamole on platelet adhesiveness aggregation or bleeding time could be demonstrated On this treatment, the mean platelet half life was close to the expected normal value but since the pretreatment survival was only slightly shortened and full normalization was the best that could be expected, statistically significant differences could not possibly be achieved by any of the drugs

ASA inhibits the platelet release reaction in vitro as well as after ingestion [10,18,33,40-43] Platelet aggregation induced by collagen and the release dependent secondary aggregation initiated by ADP or adrenalin are abolished.[18,32,33,43-46] ASA prolongs the bleeding time [18,43,47] possibly by inhibiting release and the effect of a single dose on platelet aggregation[46] and bleeding time[43] lasts for four to seven days According to Stuart,[46] the collagen induced aggregation is reduced to the same extent 15 minutes after ingestion of 0 3 Gm of ASA as after one month's treatment and the effect is the same as after a larger dose The similar effects observed on bleeding time and aggregation after the combined treatment with only 1 Gm of ASA daily and dipyridamole as after ingestion of 2 Gm of ASA can therefore be

explained by the action of this drug alone The apparent normalization of the mean platelet half life by ingestion of each drug and slight prolongation by the combined administration did not allow any conclusions Harker and Slichter[18] found no effect of ASA as opposed to dipyridamole on platelet survival It is difficult to explain why ingestion of dipyridamole in contrast to ASA, should affect platelet survival without influencing platelet adhesiveness or aggregation It can hardly be due to membrane stabilization since the degree of hemolysis was constant in our patients

Since platelets play an important role in arterial thrombus formation agents modifying their function may be effective in preventing this type of thrombosis In a double blind study Sullivan Harken, and Gorlin[49] reported that dipyridamole in a daily dose of 400 mg significantly reduced the number of thromboembolic complications in patients with prosthetic cardiac valves Since ASA reduced collagen induced aggregation considerably and inhibited the second ary irreversible aggregation in all our patients this drug might be superior to dipyridamole as an antithrombotic agent Thus Dragojevic Hetzer and Corterier[50] found that ASA in contrast to dipyridamole and warfarin effectively inhibited thrombus formation on Teflon strips implanted in dog hearts

As a consequence of the results presented, a clinical trial with ASA was started in June 1972 in a large series of patients with aortic ball valve prostheses in order to study its possible effect on arterial thromboembolism

Summary

The effects of dipyridamole and ASA on platelet functions were studied in patients with aortic ball valve prostheses Before ingestion platelet adhesiveness was markedly reduced and platelet survival time slightly but insignificantly shortened. ASA prolonged the bleeding time reduced collagen induced platelet aggregation and inhibited secondary aggregation initiated by adrenalin Similar effects were obtained with 2 Gm. of ASA alone as with 1 Gm. daily in combination with 225 mg of dipyridamole Platelet adhesiveness remained low Dipyridamole alone 375 mg daily did not influence any of these parameters. The mean platelet half life was prolonged from 3 52 to 3 72 days by each drug and to 4 days by the combined treatment None of the differences was however statistically significant. A clinical study with ASA has been started in a larger series of patients to evaluate the effect on arterial thromboembolism

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May

Frequency response of fluid-filled catheter-micromanometer systems used for measurement of left ventricular pressure

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Kenneth M Rosen M D
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Detailed analysis of left ventricular pressure waveforms requires that recordings be obtained with the least possible distortion This is best accomplished with catheter tip manometers because of their excellent dynamic response characteristics and minimal motion artifact compared to fluid filled catheter systems. However the catheter tip manometers have features which discourage routine use they are expensive easily damaged subject to zero drift require a reference manometer and must be exchanged with conventional fluid filled catheters for angiography These disadvantages and the recent availability of external micromanometers with minute displacements and excellent frequency responses have prompted us to reconsider fluid filled catheter systems to obtain high fidelity pressure curves This study presents the frequency response characteristics of five such fluid filled cardiac catheters connected to a microdisplacement solid state pressure gauge in place of the conventional manometer with a flushing dome

Materials and methods

A wide range pressure generator (Fig 1) used to test the catheter manometer systems consisted of a modified public address compression driver (University Sound Model 1D 60) and an acrylic chamber To construct the generator the phasing plug covering the diaphragm/voice coil assembly was removed (Fig 2) the pin hole in the diaphragm was sealed with a small drop of epoxy and the convex surface of the diaphragm was coated with a thin layer of epoxy to improve its water resistance The diaphragm/voice coil assembly and the magnet from the driver were then bolted to the chamber with a neoprene gasket for a seal The chamber consisted of a ½ inch thick top plate with a fitting to introduce the catheter under test a luer fitting to fill the chamber with water and to evacuate air and a third fitting for attachment of a reference manometer The cylinder was 2 inches high 2½ inches in outer diameter and 2 inches in inner diameter The bottom plate was ¼ inch thick and had been bored to the same inner diameter as the cylinder The cylinder was sealed to the top and bottom plate surfaces with high vacuum silicone grease

The pressure generator was excited with a voltage input current output power amplifier (Hewlett Packard Model 6824A) with a function generator as the signal source The constant current output from the power amplifier made the generated pressure independent of the wire temperature in the voice coil resulting in a minimum distortion of the generated pressure The frequency response of the pressure generator below 10 Hz was tested by mounting a pressure gauge directly on one of the luer fittings and recording its output with a physiologic carrier amplifier (Hewlett Packard Model 350 1100C) and recorder (Hewlett Packard Model 4560) The frequency response above 10 Hz was tested with

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Table I Catheter dimensions

Catheter type	*French size*	*Length (cm.)*	*Inner diameter (cm.)*	*Wall thickness (cm.)*	*Construction material*
Stanford pigtail	6 7	100	0 150	0 038	Polyethylene
Torcon pigtail	7	100	0 116	0 058	Steel braided Polyethylene
Gensini†	7	100	0 147	0 043	Teflon
Lehman ventriculography†	7	100	0 147	0 043	Woven Dacron
Transseptal†	8 5	69	0 151	0 066	Teflon

The dimensions and materials listed were obtained from the catalogs provided by the manufacturers
Cook Incorporated.
†United States Catheter and Instrument Corporation.

Table II Results from sine wave response

Catheter type	*n*	*fr in Hz. mean ± S D*	*RA distortion frequency*		*E (dynes/cm.⁵) × 10⁸*
			+5% Hz.	*+10% Hz.*	
Stanford pigtail	8	78 ± 6	13	21	18
Torcon pigtail	5	104 ± 7	18	26	54
Gensini	9	109 ± 5	20	26	37
Lehman ventriculography	8	114 ± 7	23	32	41
Transseptal	8	149 ± 6	29	43	45

n = the number of catheters tested in each group
fr = the resonant frequency expressed as the mean ± one standard deviation
RA = the frequency at which the amplitude response deviated +5 per cent and +10 per cent from the amplitude at 1 Hz. measured from the average amplitude frequency curve for each catheter type
E = volume modulus of elasticity

mined after each flush With repeated flushes, the resonant frequency tended to increase to a maximum value When it remained at this value within ± 2 Hz. for 20 minutes the catheter manometer system was considered to be essentially free of entrapped air bubbles The sine wave response of the catheter manometer system was recorded at intervals of 10 Hz. from 1 to 100 Hz and at intervals of 20 Hz from 120 to 200 Hz. with paper speeds from 25 to 200 mm per second.

Seven of the 38 catheters tested were used to provide a comparison between the micromanometer (MS 5) and the conventional pressure gauge (Statham P23Db) After recording the sine wave response the micromanometer was replaced with a conventional pressure gauge The system was flushed and the sine wave response recorded in the same manner as with the micromanometer

The sine wave response of each catheter was converted to relative amplitude (RA) which is defined as the ratio of the catheter manometer system amplitude at any frequency to its amplitude at 1 Hz. The frequencies at which the amplitude deviated +5 per cent (RA = 1 05) and +10 per cent (RA = 1 10) were measured from the mean amplitude frequency curve for each catheter type The volume modulus of elasticity (E) was calculated for each catheter type using the average resonant frequency [1,2] It is a measure of the stiffness of a catheter manometer system and decreases as the compliance increases

$$E = 64 \pi \rho L f^2 / 3d^2$$

Where

$E = \Delta P / \Delta V = (\text{dynes/cm}^2)/\text{cm}^3$
ρ = Fluid density in Gm /cm³
L = Catheter length in centimeters
d = Catheter inner diameter in centimeters
f = Resonant frequency in Herz

Results

Table II presents the average resonant frequency ± one standard deviation of each group

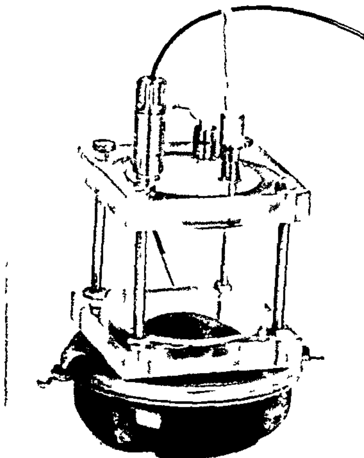


Fig 1 Pressure generator used to determine frequency responses of catheter manometer systems An MS 5 microdisplacement pressure manometer is shown mounted directly on a female luer fitting and an SF 1 catheter tip manometer is positioned near the center of the chamber

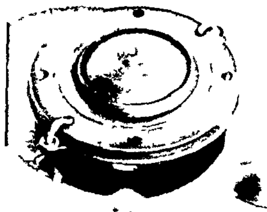


Fig 2 Driver magnet and diaphragm/voice coil assembly with phasing plug removed.

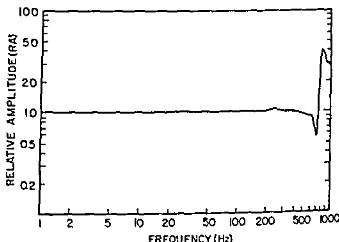


Fig 3 Pressure amplitude frequency curve of the pressure generator measured with a Statham SF 1 catheter tip manometer The first resonance of the diaphragm assembly occurred at approximately 700 Hz

a Statham SF 1 catheter tip pressure gauge approximately centered in the chamber The SF 1 was carefully flushed and was excited with 5 volts of direct current The output was observed directly on a high sensitivity oscilloscope (Hewlett Packard 130C) and photographed

The response of the pressure generator was within 3 per cent from 0 001 to 200 Hz within 5 per cent from 200 to 300 Hz and within 10 per cent from 300 to 500 Hz A typical response curve with the Statham SF 1 gauge centered in the chamber is shown in Fig 3 Driven with 2 amperes peak to peak, the generator develops approximately 40 mm Hg pressure

Since the pressure generator response was essentially flat beyond 200 Hz the generator and the SF 1 were used to measure the combined response of the carrier amplifier and light beam recorder that were used to test the catheter manometer systems The sine wave response of the catheters was corrected for the attenuation shown in Fig 4

Five commonly used catheters were studied they are described in Table I Each catheter was connected to a microdisplacement solid state pressure gauge (MS 5 Ailtech Calif) with a plastic disposable 3 way stopcock (Becton Dickinson) or a metal stopcock with a Teflon bore (United States Catheter and Instrument Corporation) The catheter manometer system was flushed with deaerated saline, and the tip of the catheter was centered in the fluid filled chamber of the pressure generator The catheter was arranged to form a coil approximately 20 cm in diameter and was covered with a towel to minimize vibration during recording The resonant frequency which is defined as the frequency at which maximum amplitude occurs was deter

of Teflon (low compliance) had an average resonant frequency of 149 Hz. The Gensini and Lehman Ventriculography catheters have the same dimensions and are both constructed of stiff material. Their average resonant frequencies differed by only 5 Hz. The resonant frequency is also increased by increasing the inner diameter of the catheter; consequently the Torcon pigtail, which had the smallest inner diameter, had the second lowest resonant frequency. The effect of system compliance on resonant frequency is also demonstrated in Table III which compares the micromanometer and conventional pressure gauges. The marked increase in the resonant frequency with the micromanometer can be attributed almost entirely to its much stiffer diaphragm and the absence of a chamber between the catheter and the transducer. The manufacturer's reported compliance expressed as volume displacement of the micromanometer (MS 5 Alltech, Calif.) is 0.0006 mm^3 per 100 mm Hg; the volume displacement of the conventional pressure gauge (Statham P23Db) is 0.04 mm^3 per 100 mm Hg, which is nearly 70 times greater.

The factors which tend to increase resonant frequency unfortunately tend to lower the damping ratio. All five catheter manometer systems had very low damping ratios; as a result, their response to a sudden change in pressure is characterized by a large overshoot followed by aftervibrations which decay exponentially to the new baseline pressure. This problem can be reduced by introducing an active electronic filter. For this purpose, the Butterworth low pass electronic filter characterized by a flat amplitude response with a sharp cutoff has been studied in vivo at various cutoff frequencies.[6] The Bessel filter is also suitable and is characterized by a linear phase shift and an amplitude roll off that is inversely related to the initial amplitude response of the catheters.

In addition to flat amplitude response, a catheter manometer system must also have a linear phase shift. We were unable to accurately measure the phase shift; however, the theoretical phase shift was calculated and found to be linear for all five catheters to the 10 per cent amplitude distortion level.

The bandwidth or frequency range of the catheter manometer system must be wide enough to include all the significant frequency components of the left ventricular pressure wave. Measurements by Fourier analysis[5,7] indicate that with normal human heart rates the significant frequency components occur within the range from 0 to approximately 25 Hz. The catheters which have a flat response to the 10 per cent level in this range are the Torcon pigtail, Gensini, Lehman Ventriculography, and Transseptal catheters.

It must be emphasized that the frequency response characteristics of these catheters in vivo will approach the results presented only if scrupulous attention is paid to eliminating minute air bubbles from the system, since they can greatly increase the system's compliance. Although not always practical, flushing the catheter manometer system with carbon dioxide before introduction of deaerated saline and the use of wetting agents such as alcohol and a detergent (detergicide USCI) have all been experimentally used to improve frequency response.[1,4,5,8] In addition, extension tubing, leaky connections, and extra stopcocks must be avoided, since all these factors tend to lower the resonant frequency of the system.

Summary

The resonant frequencies of five commonly used fluid filled catheters connected to a solid state microdisplacement pressure gauge were 18 to 33 per cent higher than those obtained with a conventional manometer. Four catheters had a flat amplitude response to 26 Hz or more at the 10 per cent amplitude distortion level. The dynamic response characteristic of certain fluid filled catheters used with microdisplacement pressure gauges allows one to record high fidelity left ventricular pressure curves.

We wish to acknowledge Mr. Brian Harris for his design of the Pressure Generator and technical advice.

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Table III Effect of P23Db and MS 5 pressure gauges on resonant frequency

Catheter type	Resonant frequency (Hz.)		Per cent increase
	P23Db	MS 5	
Stanford pigtail	64	78	18
Torcon pigtail	67	98	32
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Gensini	80	109	27
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Lehman ventriculography	85	117	27
Transseptal	105	156	32
			Average = 28

$$\text{Per cent increase} = \frac{fr(MS\ 5)\ fr(P23Db)}{fr(MS\ 5)} \times 100$$

of catheters tested The amplitude response was flat to at least 26 Hz at the 10 per cent level of distortion with all catheters except the Stanford pigtail The calculated volume modulus of elasticity demonstrated that the Torcon pigtail catheter is the least compliant, and the Stanford pigtail the most compliant

A mean amplitude frequency curve for each catheter type is shown in Fig 5 It is evident from these curves that catheters with higher resonant frequencies have a more prolonged flat frequency response The transseptal catheter which had the highest resonant frequency had a flat response to 43 Hz at the 10 per cent level The Stanford pigtail which had the lowest resonant frequency was flat to only 21 Hz

A comparison of the resonant frequencies of seven catheters utilizing the micromanometer and the conventional pressure gauge are displayed in Table III The resonant frequency increased from 18 to 33 per cent with an average increase of 28 per cent when the micromanometer was used

Discussion

The dynamic response characteristics of a catheter manometer system that is required to faithfully reproduce a pressure wave include flat amplitude response linear phase shift, and an adequate bandwidth Since the flat amplitude response is extended when the resonant frequency is increased it is advantageous within limits to choose a catheter manometer system with a high resonant frequency

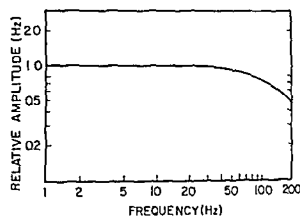


Fig 4 Pressure amplitude frequency curve of Hewlett Packard carrier amplifier and light beam recorder measured with an SF 1 catheter tip manometer

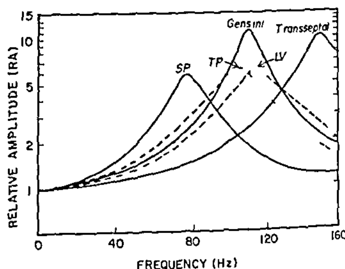


Fig 5 Average pressure amplitude frequency curve of each catheter type connected to the micromanometer via a three-way plastic stopcock The Stanford pigtail curve (SP) is an average of n = 8 catheters Torcon pigtail (TP) n = 5 Gensini n = 9 Lehman Ventriculography (LV) n = 8 and Transseptal n = 8

Many factors affect the resonant frequency of a fluid filled system including the catheter dimensions and the compliance of the system It has been demonstrated that the resonant frequency is increased by decreasing the catheter length and the compliance of the system[2,4] The Stanford pigtail which is a 100 cm long thin walled catheter made of polyethylene (high compliance) had an average resonant frequency of only 78 Hz, whereas the Transseptal which is 31 cm shorter and is a thick walled catheter made

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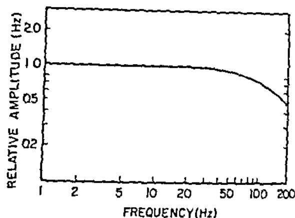


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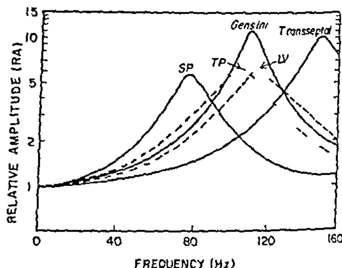


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A new method for determination of postmortem left ventricular volumes clinico-pathologic correlations

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J Al Sadir M D
S Glagov M D
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Progress made in clinical cardiology during recent years, based on both invasive and noninvasive techniques challenges the pathologist to develop more refined methods of postmortem examination of the heart [1,2] Particularly needed are techniques for accurate measurement of several heart parameters including exact size of myocardial infarction ventricular mass and ventricular volume

Recently Glagov Eckner and Lev[3] have developed procedures which allow fixation of the heart in its diastolic contour by perfusion of the coronary arteries using a pressure that is near the diastolic pressure in vivo This technique is used routinely in our study of the Myocardial Infarction Research Unit (MIRU) hearts [1] It facilitates several measurements [4] and includes a simple technique for accurate estimation of postmortem diastolic ventricular volume following fixation This report will describe this technique and offer preliminary evidence of its usefulness for documenting a rather constant finding in the hearts of patients who succumb during cardiogenic shock

Method

After careful flushing of both ventricles with saline to remove postmortem clots the hearts are fixed for 3 to 4 hours using Glagov Eckner and Lev s[3] apparatus This involves perfusion with 10 per cent neutral buffered formalin through an aortic cannula Another cannula is inserted in the pulmonary artery Perfusion pressures used are 100 to 120 mm. Hg for the aorta and 20 mm. Hg for the pulmonary artery The heart is then disconnected from the pressure apparatus and left suspended in formalin for an additional 24 hours, after which it is rinsed thoroughly in water and each ventricle is filled with Silastic* or comparable dental impression material [1,2]

The material is prepared just before using by adding hardener to Silastic (The amount required is 150 to 300 c c depending on the size of the heart)

The material is left to harden overnight and the heart is then sliced at 1 cm intervals from the apex to the tricuspid or mitral valve ring (Fig 1) The hardened Silastic is carefully removed from each ventricle with special attention to exclude any material that escaped into the atria The ventricular volume is then determined by water displacement in a graduated cylinder The only problems noted are the inaccuracy produced by extensive mural thrombosis and the occasional incomplete filling of the ventricles by the Silastic The latter can generally be avoided with experience

Results

We have now used this method to measure the ventricular volumes in numerous postmortem

F om the Dep rtment f Pathology and Internal Med ine The Univers ty of Ch cag Chicago

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*Silastic 502 RTV Silicone Pubber obtained f om Dow Corning Midland, Mi h. and Silast RTV 21 Liquid Sil cone Rubber obtained from Gener l Flectric—Silicone Products Department, Waterford, N Y hav been used in these stud es.

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4) and small stroke volumes (measured by the dye dilution technique) Clinical data indicate that most of these patients were in cardiogenic shock for several hours before death

As Table I shows all other ventricular volumes varied from 30 to 52 ml Of these cases all were in *MIRU* clinical Classes 1 or 2 except for Patients No 9 and No 14 In Patient No 9 there was no evidence of coronary artery disease, but the presence of cerebral infarction, severe bronchopneumonia hypoxia and metabolic acidosis can explain his low output state Patient No 14 was admitted to the hospital with extensive acute myocardial infarction and intractable cardiogenic shock He underwent intra aortic balloon counterpulsation (IABP) for 10 hours and was taken in this condition to the cardiac catheterization laboratory Death occurred during coronary arteriography The normal left ventricular volume was partially due to the left ventricular unloading by IABP and possibly also to the fact that the patient died less than 24 hours after the acute episode

Discussion

This simple method appears to be useful for documenting the anatomic characteristics of a failing heart in which the myocardium is not capable of contracting sufficiently to produce the usual postmortem contracted left ventricle Left ventricular volume measurements can be obtained by other methods but we doubt if any are as simple accurate and easy For instance it is difficult to measure ventricular volume accurately by filling the ventricles with water or other liquids because the liquids tend to pass through the valves producing either high or low results

A point counting method is also being tested in our laboratory by means of a graduated grid superimposed over each slide of the heart (Fig 2) Total ventricular volume is obtained by integrating the volumes of all the slices This method is also easy and not very time consuming if the grid is a large one (0 5 to 1 cm) but it is probably less accurate than the Silastic method described here

The results document an interesting exception to the largely accepted Starling s law of the heart[5] which says within physiologic limits a larger diastolic cardiac volume results in a

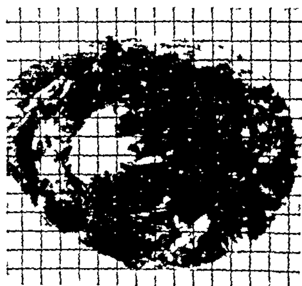


Fig 2 Heart sliced as in Fig 1 but with Silastic removed. Plastic transparent grid superimposed over heart allows point counting of the ventricular cavity The light areas in the cross section of the myocardium are presumed areas of ischemia resulting in dehydrogenase loss

greater energy of contraction and a greater amount of chemical changes at each contraction It appears that with increasing inflow and increasing diastolic volume the crest of augmented cardiac output is reached and passed. Further increments in venous return can overload and distend the weakened heart and cardiac output is decreased.

In fatal congestive heart failure the physiologic limits are passed and cardiac output is inadequate despite dilation of the ventricle or ventricles The heart continues to dilate and pronounced degrees of ventricular failure are seen with very low stroke volumes and critical clinical conditions

Results obtained with these casts or molds of the left ventricle have confirmed this correlation between large ventricular volume and clinical evidence of low cardiac output and cardiogenic shock Furthermore the simplicity and accuracy of this new method for postmortem measurement of ventricular volume facilitates investigation of the pathogenesis of severe cardiac dilation and suggests studies correlating ventricular volume with other parameters such as the severity of acute myocardial ischemia the amount of irreversible myocardial damage and with various changes in the conduction system



Fig 1 Shows the hardened silicone rubber mold of the right and left ventricles The heart was sliced at 1 cm intervals from apex to base The dark areas in the ventricles have been stained with nitroblue tetrazolium

Table I Correlation between postmortem ventricular volume and clinical data

Series No	*Autopsy No*	*Heart weight (grams)*	*Ventricular volume (mL)*		*Antemortem stroke volume (mL)*	*MIRU clinical evaluation*
			Right	*Left*		
1	15979	550	45	52	35	2
2	16254	520	56	46	70	1
3	16504	830	60	110	22	3 4
4	16745	560	62	110	18	4
5	16853	560	25	100	10	3 4
6	16889	910	52	60	29	4
7	16882	580	43	40	61	2
8	17054	575	48	110	21	4
9	17116	360	40	40	22	4
10	17119	565	75	83	22	4
11	17125	500	27	97	14	4
12	17177	605	128	90	24	4
13	17229	995	36	72	34	2
14	17436	450	65	47	12	4
15	17512	550	73	33	72	1

specimens of the heart Table I surveys the results from 15 hearts in which the antemortem hemodynamic studies including measurement of stroke volumes (Normal 50 to 60 ml per beat) were made Cases were classified according to the MIRU clinical classification in which Class 1 includes those without heart failure, Class 2, those with minimal failure, Class 3 those with severe failure and Class 4 those with cardiogenic shock In six cases, antemortem hemodynamic studies were made within 48 hours before autopsy Seven patients were classified several days before death and remained in the same MIRU classification throughout this period Patient No 2 had no complications during hospitalization until he died of dysrhythmia just prior to discharge whereas Patient No 8 was admitted in cardiogenic shock showed signs of improvement and then died several weeks later again in cardiogenic shock

Almost all of the specimens in which the postmortem left ventricular volume was over 60 were from cases which exhibited severe heart failure or cardiogenic shock (MIRU Classes 3 or

Case reports

Bacteroides pericardial effusion and cardiac tamponade in a patient with chronic renal failure

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Approximately 30 to 50 per cent of patients with uremia develop pericarditis[1-3] This uremic pericarditis is basically fibrinous in nature and is usually not associated with pericardial effusion[4] In recent years there has been increasing recognition of effusive pericarditis massive hemorrhagic pericardial effusion cardiac tamponade and chronic constrictive pericarditis as complications of the uremic state[3-8] Furthermore secondarily infected uremic pericardial effusions have been noted in a few subjects[8]

We describe here cardiac tamponade secondary to Bacteroides induced purulent pericardial effusion in a patient with chronic renal insufficiency

Case report

A 31 year-old Papago Indian woman (GSH No 181 680) was referred to the Good Samaritan Hospital for evaluation of pericardial effusion Ten years previously the patient was noted to have diastolic arterial hypertension. In 1966 her blood urea nitrogen was 30 mg per 100 ml and serum creatinine 3 mg per 100 ml. In November 1971 the patient entered another hospital with anemia azotemia pericarditis and a blood pressure of 180/110 mm. Hg Peritoneal dialysis was subsequently instituted and performed intermittently over the next four months by means of permanently implanted Tenckhoff tube In February 1972 the patient was noted to have purulent drainage from the dialysis catheter and recurrent pericarditis At that time the blood urea nitrogen was 123 mg per 100 ml and serum creatinine 18 mg per 100 ml Culture of the peritoneal dialysate revealed a heavy growth of *Pseudomonas aeruginosa*. Hemodialysis was then started Subsequently the patient developed abdominal pain and physical signs of peritonitis Exploratory abdominal surgery was then performed. Laparotomy revealed extensive peritoneal adhesions a small bowel perforation, a localized intraperitoneal abscess and, in proximity to the abscess, a small fragment of the Tenckhoff tube which had apparently broken off at an earlier date The adhesions were lysed, the perforation closed, the abscess drained and the foreign body removed Intravenous gentamycin and carbenicillin were administered. Over the next month the patient experienced weakness and shortness of breath. The blood pressure declined to 120/90 mm Hg with an inspiratory systolic reduction of 25 mm Hg Serial chest roentgenograms demonstrated progressive enlargement of the cardiac silhouette A cardiac scan was compatible with the diagnosis of pericardial effusion

On admission to the Good Samaritan Hospital the temperature was 99 8° F pulse 100 per minute, and blood pressure 110/70 mm Hg with a paradoxical pulse of 15 mm Hg During inspiration there was marked distention of the neck veins. Precordial percussion demonstrated increased flatness 3 cm lateral to the left midclavicular line Cardiac auscultation revealed muffled heart sounds Laboratory data were as follows: multiple blood cultures revealed no growth hemoglobin 7 4 Gm. per 100 ml. hematocrit, 21 per cent leukocyte count 18,500 per cubic millimeter blood urea nitrogen 42 mg per 100 ml. serum creatinine 4 7 mg per 100 ml. sodium 133 mEq per liter potassium 3 4 mEq per liter chloride 88 mEq per liter and CO_2 content 19 mEq per liter An electrocardiogram showed nonspecific S T segment and T wave changes. A chest roentgenogram demonstrated a markedly enlarged cardiac silhouette (Fig 1) Right and left heart catheterization was performed. Pericardial effusion was suspected when the catheter was advanced to the right atrium and a large distance seen between the right heart border and the catheter tip in contact with the atrial endocardium Right heart angiography indicated the presence of pericardial effusion (Fig 2) Right and left heart pressures (in millimeters of mercury) were as follows right atrium (mean) = 18 right ventricle (systolic/end diastolic) = 36/20 pulmonary artery (systolic/diastolic/mean) = 32/20/26 mean pulmonary arterial wedge" = 24 left ventricle (systolic/end diastolic) = 117/30 ascending aorta (systolic/diastolic) = 117/60 the cardiac index was 1 4 L. per minute per square meter These latter hemodynamic findings were indicative of either cardiac compression by effusion and/or restrictive myocardial disease Two days later the pa

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Summary

A description is presented of a new and simple *procedure for ventricular volume determination* by means of pressure fixation of the heart and preparation of plastic molds of the ventricles which can be used to displace water in a gradu ated cylinder to determine the volume of the mold

Correlations between postmortem ventricular volume as measured by this method and an temortem stroke volume or clinical cardiac sta tus indicate that a large left ventricular volume is often correlated with a low cardiac output and cardiogenic shock

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thrombophlebitis Generalized Bacteroides septicemia has been known to arise from throat infection otitis media, mastoiditis surgical infections ulcerations of the gastrointestinal tract war wounds or infected and traumatized female reproductive organs [12,25] When Bacteroides enters the circulatory system metastatic abscesses may develop in the brain lung liver and joints However to our knowledge there has been no previous report of culturally proved Bacteroides infection of the pericardium McVay and Sprunt[16] reviewed 35 cases of Bacteroides infection and noted that a single patient with multiple pulmonary abscesses had 75 ml. of serous fluid in the pericardial sac at postmortem examination No mention was made concerning bacteriologic examination of this fluid. In a report of 25 instances of Bacteroides septicemia Tynes and Frommeyer[18] described a patient who developed a pericardial friction rub acute renal failure and Bacteroides peritonitis following a sigmoid colon resection This latter case probably represented pericarditis as a complication of uremia,[4] although seeding of the pericardium by bacteria may have occurred. Janecka and Rankow[21] reported a patient who developed acute gangrenous mediastinitis secondary to Bacteroides pharyngitis At postmortem examination the pericardium was described as being covered with a collagenous membrane but apparently there was no pericardial effusion Forbes and Goligher[25] described a subject with posttraumatic Bacteroides bacteremia who was found to have multiple metastatic foci of infection including a pulmonary abscess and pleural effusion Autopsy in this patient demonstrated a pericardial effusion but there was no statement regarding cultural characteristics of the fluid. In his review of Bacteroides infection Gunn[24] noted nine instances of pericardial effusion bacteriologic examination was not reported. It is possible that some of the above cases represented unrecognized Bacteroides pericarditis Myocardial abscess[26] and endocarditis[12,14,29] are other recognized cardiac complications of Bacteroides infection.

Given a patient with chronic renal insufficiency the development of an enlarging cardiac silhouette a fall in blood pressure distended neck veins and other signs of a low cardiac output state are strongly suggestive of hemorrhagic pericardial effusion with cardiac tamponade [3-5] The level of systolic and diastolic blood pressures may be misleading since previously elevated values may fall into the normal range as a consequence of the cardiac compression Although such hemorrhagic effusions are usually sterile on culture it is noteworthy that Skov Hansen and Spencer[5] reported two patients with chronic renal failure who developed purulent staphylococcal pericardial effusions with cardiac tamponade General debilitation along with commonly employed diagnostic and therapeutic measures are believed to play important roles in the propensity of patients with chronic renal disease to develop local and generalized infection [27] Suppression of the inflammatory response reduction of lymphoid or macrophage reactivity and blunting of immunologic responsiveness have all been noted in uremic subjects [28]

Effective treatment of purulent pericardial effusion with tamponade is based on a combination of appropriate cultures antibiotics and surgical drainage of the pericardium It is important that such cultures be performed anaerobically in the event that organisms such as Bacteroides are the offending agents Although most anaerobic cultures containing Bacteroides will reveal organisms within 48 hours some may require 10 to 18 days for growth Thus all anaerobic cultures should be left intact for at least three weeks before they are considered negative [12,17,18]

Previously there was some controversy regarding the antibiotic of choice in the treatment of Bacteroides infection Gillespie and Guy[23] found that 100 per cent of Bacteroides isolates from purulent exudates were sensitive to tetracycline and chloramphenicol In Bodner Koenig and Goodman's[12] experience 26 per cent of Bacteroides cultures were resistant to tetracycline but sensitive to chloramphenicol. On the other hand, Tynes and Frommeyer[18] described three isolates of tetracycline sensitive Bacteroides which were resistant to chloramphenicol. Sinkovics and Smith[20] demonstrated 25 per cent of Bacteroides strains resistant to tetracycline which were sensitive to chloramphenicol In acute clinical situations pending definitive antibiotic sensitivity tests clindamycin appears to be the treatment of choice for life threatening Bacteroides infections This latter drug has been demonstrated to be almost uniformly effective in severe bacteroides infections and is therapeutically efficacious when ad



Fig 1 Postero anterior chest roentgenogram demonstrates enlargement of the cardiac silhouette in its transverse diameter

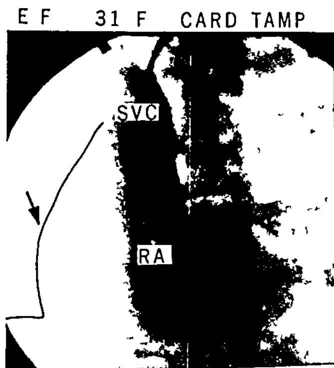


Fig 2 Superior vena cava (SVC) right atrial (RA) angiogram in a 31 year old woman with purulent pericardial effusion and cardiac tamponade The right heart border has been retouched (arrow) for the purpose of illustration Note the marked distance between the right atrial cavity and the right heart silhouette indicating pericardial effusion.

tient was subjected to pericardiectomy At surgery 1 500 ml of foul smelling purulent material was drained from a distended pericardial sac Multiple anaerobic cultures of the pericardium and its contents revealed pure growth of *Bacteroides fragiles* within 48 hours Postoperatively the patient was treated with intravenous chloramphenicol and she has had a satisfactory clinical course since that time

Discussion

Bacteria are the etiologic agents most commonly involved in the formation of purulent pericardial effusion Staphylococci pneumococci and streptococci are the organisms usually cultured from such purulent effusions [9,10] Numerous other bacteria have been recovered from purulent pericardial exudate[9,11] and they include *Neisseria meningitides N gonorrhea, Hemophilus influenzae H pertussis* Salmonella *Pasturella tularensis* Brucella, *Escherichia coli* Pseudomonas Klebsiella, Proteus, *S moniliformis* and Clostridia Fungi[9] (*Aerobacter actinomycoses* and Blastomycetes), protozoa (*Entameba histolytica*), and other parasites (*Acanthocheilonema perstans*) have also been recovered from the human pericardium These pathogenic agents usually gain access to the pericardium via contiguous spread from pneumonic infiltration mediastinitis, septicemia or rupture of an intraabdominal process through the diaphragm into the pericardial sac Purulent pericarditis has also been noted to develop from direct extension of a myocardial abscess [9] The patient described in this report probably developed Bacteroides pericardial effusion as a consequence of blood borne or contiguous spread from an intraperitoneal abscess to the pericardium which was already involved by uremic pericarditis

The genus Bacteroides is a group of nonspore forming, Gram negative, obligate, anaerobic bacilli From a clinical standpoint the significant species are *B fragilis B funduliformis* and *B melaninogenicus* [12] since they are most commonly recovered in human infection Bacteroides are normal inhabitants of the oral cavity, pharynx cervix and gastrointestinal tract accounting for 90 to 99 per cent of the normal intestinal flora of man [12,14] Under conditions involving tissue necrosis or localized abscess formation, Bacteroides may invade tissue directly or result in septic

Inter coronary steal syndrome resulting from aortocoronary bypass surgery

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Since the original description of cerebral vascular ischemia produced by reversal of blood flow in a vertebral artery[1] and coinage of the term subclavian steal[2] a number of steal syndromes have been described involving other areas of the circulation. Steal phenomena causing regional ischemia have been reported involving the thyrocervical[3] mesenteric[4] aorto iliac[5,6] external carotid,[7] and coronary arteries[8-11] The term coronary steal, has been applied to situations in which (1) shunting of blood occurs from implanted internal mammary arteries via a capillary network to pulmonary vessels[9] or (2) from a normal right coronary artery through inter coronary anastomoses to a left coronary artery having anomalous origin in the pulmonary artery[12-14] In addition intramyocardial shunting of blood from diseased vessels to normal ones has been offered as an hypothesis to explain the paradoxical induction of angina by vasodilators[8,15] in some patients Though not demonstrable angiographically such shunts would help to explain otherwise confusing metabolic changes in some patients with arteriosclerotic heart disease who are given vasodilating drugs[11] The present case demonstrates another type of coronary artery steal resulting from a type of aorto coronary bypass graft

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Reprint requests to Dr Benjamin Befeler Chief Cardiovascular Laboratory Veterans Administration Hospital, Miami, Fla 33125

Case presentation

The patient (R S) is a 47 year old white male who was in good health until 1961 when he sustained an acute myocardial infarction at the age of 36 years He did well until August, 1970 when he had a second myocardial infarction. Angina dyspnea pedal edema, and occasional paroxysmal nocturnal dyspnea followed convalescence from the second infarction He was treated with digitalis and nitroglycerin His condition gradually deteriorated. Upon his third admission in July of 1972 he complained of angina, and angina at rest. Dyspnea occurred with moderate effort, paroxysmal nocturnal dyspnea was noted three times a week and persistent four pillow orthopnea despite digitalis, diuretics, salt restriction and nitroglycerin

On physical examination the patient appeared to be a well developed white man with a blood pressure of 124/70 mm Hg The pulse was 80 and regular Jugular venous pulse and carotid pulsations were normal The first heart sound was normal second heart sound had physiologic splitting An S_4 was heard at the apex but no S_3 no murmurs were detected. Abdominal examination disclosed a palpable aneurysm and peripheral pulses were strong and symmetrical in all extremities. The remainder of the physical examination was unremarkable An electrocardiogram revealed normal sinus rhythm, with old inferior and anterior wall myocardial infarctions Chest roentgenograms revealed a normal cardiac silhouette with linear calcifications of the aortic knob and posterior wall of the descending aorta No signs of congestive heart failure were noted.

Because of the severe and intractable symptoms cardiac catheterization was performed to evaluate the patient for possible vein graft bypass surgery Catheterization findings are listed in the first column of Table I The right and left ventricular end diastolic pressures were both elevated Ventriculography revealed the cavity of the left ventricle to be moderately increased in size with a reduced estimated ejection fraction Apical dyskinesis and surrounding hy

ministered by the intramuscular route[30] Regardless of the drug utilized prompt surgical drainage of the pericardium is mandatory if purulent pericarditis is suspected

This report emphasizes that cardiac compression in the presence of renal insufficiency can result from purulent as well as hemorrhagic effusion In the setting of recent intra abdominal infection, Bacteroides should be suspected as the agent responsible for this potentially lethal condition

Summary

A 31 year old woman with chronic renal insufficiency and recurrent pericarditis developed an enlarging cardiac silhouette and physical signs of cardiac tamponade Cardiac catheterization demonstrated pericardial effusion with hemodynamic evidence of cardiac compression At pericardial exploration 1 5 L of foul smelling purulent material was removed from a distended pericardial sac Cultures of both the exudate and pericardium revealed pure growth of *Bacteroides fragiles* The patient was subsequently treated with intravenous chloramphenicol and has had an uncomplicated clinical course since that time

This represents the first reported case of cardiac tamponade secondary to culturally proved Bacteroides pericarditis in the setting of chronic renal insufficiency

We wish to acknowledge the technical assistance of Nancy Copeland R N Carole Crevier Larry Kuriger Sydney Peebles Sharon Squire and Les Zendle

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Inter coronary steal syndrome resulting from aortocoronary bypass surgery

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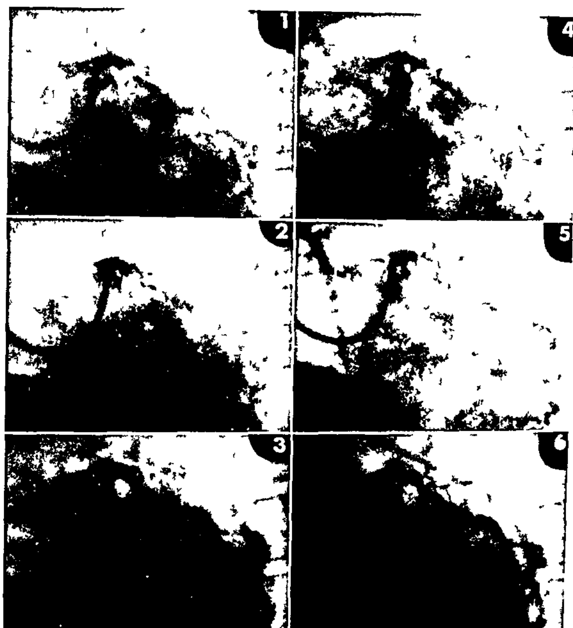


Fig 1 Selected sequence of frames from a 35 mm cineangiogram of the left coronary artery and vein grafts in the left anterior oblique 45 at 60 frames per second Note that the contrast medium runs down the circumflex branch then into one of the limbs of the Y bypass up to the bifurcation of the Y and down the other limb of the Y graft into the anterior descending artery The communication of the two limbs of the Y with the aorta is obstructed

pokinesis in the anterior apical region were present No mitral regurgitation was present Aortography revealed a tri cuspid aortic valve and trivial aortic regurgitation Coronary cineangiograms revealed complete obstruction of the right coronary artery at its origin Opacification of the left coro nary artery showed an irregular small distal right coronary artery segment which filled retrogradely The left coronary artery arose in normal fashion from the left sinus of Valsalva and bifurcated into left anterior descending and circumflex branches The left anterior descending branch was 90 per cent obstructed at the area of the first septal perforating branch The distal left anterior descending artery filled by bridging collaterals and appeared to be a recanalized vessel The left circumflex artery was large and gave off one lateral ventricular branch a large obtuse marginal branch with a proximal 90 per cent obstruction and a large posterior lateral branch Minor luminal irregularities were noted in the circumflex artery in addition to the major obtuse marginal obstruction It was concluded that the patient had mixed arteriosclerotic and rheumatic heart disease with three vessel coronary artery disease left ventricular dys function minimal aortic insufficiency and elevated end diastolic pressures in both ventricles Coronary vein graft bypass surgery was recommended

At surgery three aortocoronary vein grafts were con structed The first graft was placed between the aorta and the posterior descending branch of the right coronary artery the second to the obtuse marginal branch of the circumflex coronary artery and the third to the mid left anterior de scending artery The proximal anastomosis of two of the grafts was to the ascending aorta but the third was placed in an end to side fashion into the graft to the obtuse marginal branch forming an inverted Y The postoperative course was uneventful and the patient went home

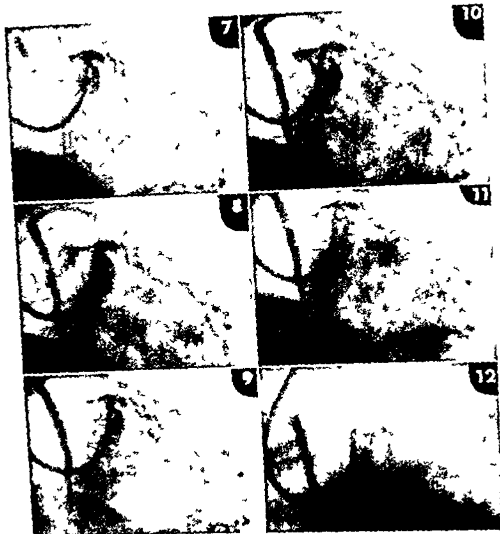


Fig. 1 continued. For legend see opposite page.

After convalescence from surgery the patient reported marked decrease in both symptoms of failure and angina on digoxin and a 2 Gm. salt diet. When readmitted for postoperative catheterization five months after surgery he was completely free of angina. He denied dyspnea with ordinary activities or orthopnea. Physical examination revealed a blood pressure of 130/80 and a pulse of 72 and regular. A grade II/VI systolic crescendo-decrescendo murmur was present along the left sternal border and at the apex. A faint decrescendo early diastolic murmur was also noted. An anterior systolic outward movement of the precordium over the fourth and fifth intercostal spaces above the apex was noted and an S_4 was heard at the left sternal border. The remainder of the physical examination was unchanged. Hemodynamic measurements obtained during the second catheterization are listed in Column 2, Table I. All pressures are within normal limits. Angiography of the left ventricle revealed no change in size of cavity but contractions appeared improved except for the antero-apical region which remained dyskinetic. The proximal right coronary artery was totally occluded as before. A patent aortocoronary bypass graft extended from the aortic root to the posterior descending branch of the right coronary artery and it was selectively opacified. The left anterior descending branch of the left coronary artery was totally occluded in the area previously subtotally occluded near the first septal perforator. The circumflex coronary artery was unchanged in appearance with the previously noted 90 per cent obstruction in the proximal obtuse marginal branch. The proximal (aortic) end of the inverted "Y" graft could not be opacified. Opacification of the left coronary artery revealed sequential filling of the following vessels: the main trunk, proximal circumflex, obtuse marginal branch, aortocoronary bypass graft to the obtuse marginal branch, retrograde flow to the area of the end to side anastomosis with the bypass to the left anterior descending and antegrade flow in the left anterior descending bypass graft to the left anterior descending distal segment (Figs. 1 and 2).

The patient was discharged from the hospital the following day for continued medical management.

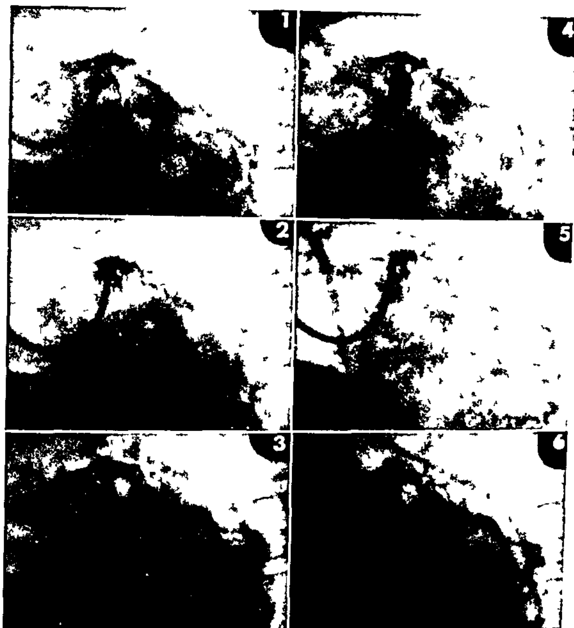


Fig 1 Selected sequence of frames from a 35 mm cineangiogram of the left coronary artery and vein grafts in the left anterior oblique 45 at 60 frames per second. Note that the contrast medium runs down the circumflex branch then into one of the limbs of the Y bypass up to the bifurcation of the Y and down the other limb of the Y graft into the anterior descending artery The communication of the two limbs of the Y with the aorta is obstructed

pokinesis in the anterior apical region were present No mitral regurgitation was present Aortography revealed a tri cuspid aortic valve and trivial aortic regurgitation Coronary cineangiograms revealed complete obstruction of the right coronary artery at its origin Opacification of the left coro nary artery showed an irregular small distal right coronary artery segment which filled retrogradely The left coronary artery arose in normal fashion from the left sinus of Valsalva and bifurcated into left anterior descending and circumflex branches The left anterior descending branch was 90 per cent obstructed at the area of the first septal perforating branch The distal left anterior descending artery filled by bridging collaterals and appeared to be a recanalized vessel The left circumflex artery was large and gave off one lateral ventricular branch a large obtuse marginal branch with a proximal 90 per cent obstruction and a large posterior lateral branch. Minor luminal irregularities were noted in the circumflex artery in addition to the major obtuse marginal obstruction It was concluded that the patient had mixed arteriosclerotic and rheumatic heart disease with three vessel coronary artery disease left ventricular dys function minimal aortic insufficiency and elevated end diastolic pressures in both ventricles Coronary vein graft bypass surgery was recommended

At surgery three aortocoronary vein grafts were con structed The first graft was placed between the aorta and the posterior descending branch of the right coronary artery the second to the obtuse marginal branch of the circumflex coronary artery and the third to the mid left anterior de scending artery The proximal anastomosis of two of the grafts was to the ascending aorta but the third was placed in an end to side fashion into the graft to the obtuse marginal branch forming an inverted Y The postoperative course was uneventful and the patient went home

bypass grafts but this is the first instance of intercoronary shunting of blood we have seen It is the feeling of some surgeons that aortocoronary bypass grafts should not be constructed with inverted Y type anastomosis[16] though it is recommended by others[17] It is argued that the fate of the two grafts may then depend upon the technical adequacy of one anastomosis Certainly a Y type anastomosis may be susceptible to stagnant flow with subsequent thrombosis Moreover persistent patency of grafts has been related to flow rates and run off assessed reasonably accurately at the time of surgery[18] While the adequacy of flow and run off can be assessed in part by physical examination in peripheral vascular disease there are no techniques available for assessing intramyocardial run off in the distribution of diseased coronary arteries preoperatively Thus any estimation of reduced flow angiographically might be due to a variable combination of obstructions and/or poor run off It is presently believed that obstructive disease is the cause of poor coronary flow whereas small vessel disease has been suggested as the cause of poor run off by some[18] and highly contested by others It follows that assessment of flow in coronary artery bypass grafts cannot be predicted by noting the degree of coronary artery obstruction alone since it also depends upon the unmeasurable run off factor

The present patient demonstrated no increase of symptoms as a result of his intercoronary steal but the fact that the steal physiology can be created by at least this one type of vein graft bypass procedure is reason for caution We believe that it would therefore be prudent to avoid any type of coronary artery bypass graft construction which could give rise to intercoronary shunting

Finally in view of the recent questions raised concerning the value of naturally occurring collateral vessels to the patient with coronary disease[19] one wonders whether such vessels might not represent (under some conditions) a naturally occurring intercoronary steal

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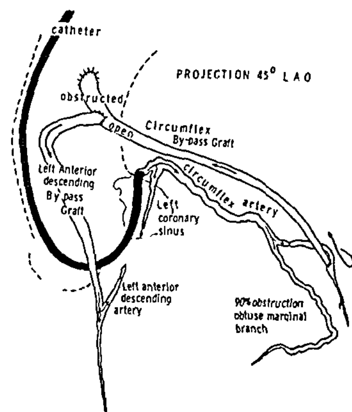


Fig 2 Diagrammatic representation of flow in the left coronary artery 45° left anterior oblique and the direction of the flow in the partially obstructed Y bypass demonstrating an intercoronary *steal syndrome*

Table I Hemodynamic measurements during catheterization*

	Preoperative	*Postoperative*
Right atrium		
Mean	6	2
A	9	2
V	7	3
Right ventricle	26/10	24/4
Pulmonary artery	26/13	21/9
Mean	19	
Pulmonary artery wedge		
Mean	10	4
A	12	5
V	14	7
Left ventricle	121/14	142/10
Aorta	115/63	142/82
Mean	83	105
Cardiac output (L/min)	5 40	5 30
Cardiac index (L/min/m²)	3 10	3 06
Pulmonary vascular resistance (dynes/sec/cm⁻⁵)	138	106
Systemic vascular resistance	1 181	1 560

All pressures are given in millimeters of mercury

Discussion

The sequence of opacification shown in Fig 1 is diagrammatically represented in Fig 2 The net result is a redistribution of blood flow from the obtuse marginal branch to the distal left anterior descending artery via the arcade of saphenous vein bypass grafts Thrombosis of the proximal portion of aortocoronary bypass graft to the obtuse marginal branch had occurred at some time in the postoperative period

The essential anatomic characteristics of a vascular steal consist of a major vascular communication between two arterial circuits Should flow be decreased in the runoff distribution of one system, it can then be shunted through the communicating vessel to the other system for run off in its lower resistance distribution [2] Since both ends of the saphenous vein arcade were placed at points distal to high grade obstruction one can reasonably conclude that the resistance to run off in the distal circumflex system was greater than the resistance to run off in the left anterior descending system, thereby causing blood to flow from the distal circumflex to the left anterior descending The total coronary flow in this patient pre or postoperatively is unknown Indeed, it has been shown that patients with arteriosclerosis and coronary obstructive disease have a total artery flow which is similar to normal subjects at rest [15] Our patient experienced a remarkable hemodynamic and symptomatic improvement as a result of surgery His exercise tolerance was markedly improved and diuretics salt restriction and nitroglycerin were stopped. It is probably safe to assume that flow was improved to the distal segment of the right coronary artery through the patent aorto right coronary bypass graft The total flow in the left coronary artery system may or may not have changed as a result of surgical intervention However in both pre and postoperative studies, flow going to the left coronary system originated from the left coronary ostium but the vascular arcade shunting blood from the circumflex to the left anterior descending artery likely decreased myocardial perfusion in the distribution of the circumflex artery in favor of flow to the anterior descending system

In reviewing the angiograms from other patients who have undergone aortocoronary bypass surgery, we have seen many examples of altered flow patterns such as retrograde flow in patent bypass grafts patency of grafts with bidirectional pulsatile flow and reversal of flow in

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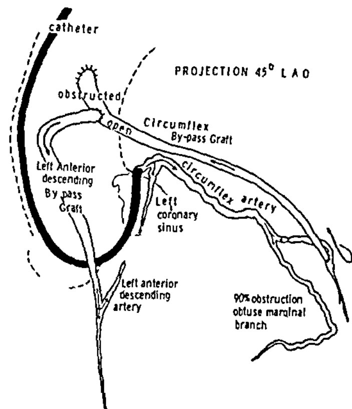


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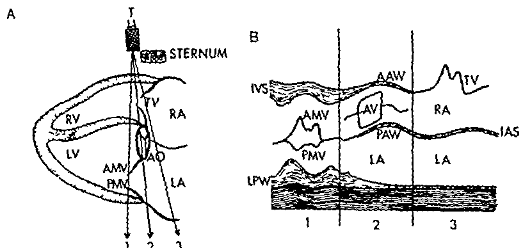


Fig 1 Diagrammatic representation of a cross section of the heart illustrating the location of intracardiac structures encountered during angulation of the transducer rightward and superiorly through positions 1 2 and 3 (A) Positions 1 2 and 3 indicate location of mitral valve (AMV PMV) aortic root (Ao) and tricuspid valve (TV) Abbreviations LA left atrium RA right atrium LV left ventricle RV right ventricle T transducer AMV anterior mitral valve and PMV posterior mitral valve In B a diagrammatic representation of the echocardiogram in positions 1 2 and 3 is shown As the transducer is angulated from position 1 to 2 the interventricular septum (IVS) merges into the anterior aortic wall (AAW) which eventually becomes contiguous with the tricuspid valve (TV) in position 3 The anterior and posterior mitral valve (AMV PMV) is contiguous with the posterior aortic wall (PAW) as the transducer is angulated from position 1 to 2 Abbreviations LPW left ventricular posterior wall LA left atrium RA right atrium and IAS interatrial septum

Table II Echocardiographic criteria for normal newborn infants*

Pulmonary artery diameter (mm.)	
Range	9 4 – 13 0
Mean ± SE	11 1 ± 0 2
Aortic room diameter (mm.)	
Range	8 1 – 12 0
Mean ± SE	10 0 ± 0 06
Left atrial diameter (mm.)	
Range	5 0 – 10 0
Mean ± SE	7 0 ± 0 1
Interventricular septal thickness (mm.)	
Range	1 8 – 4 0
Mean ± SE	2 7 ± 0 04

From Hagan, A D Deely W J Sahn, D and Friedman, W F Echocardiographic criteria for normal newborn infants Circulation 48 12 1 1973

Table III Echocardiographic criteria for normal newborn infants*

	Right ventricle	Left ventricle
End systolic wall thickness (mm)		
Range	3 3 – 7 3	2 5 – 6 0
Mean ± SE	5 0 ± 0 1	4 3 ± 0 1
End diastolic wall thickness (mm.)		
Range	2 0 – 4 7	1 6 – 3 7
Mean ± SE	3 0 ± 0 1	2 6 ± 0 1
End systolic diameter (mm.)		
Range	5.5 – 11 4	8 0 – 18 6
Mean ± SE	9 4 ± 0 2	13 3 ± 0.3
End-diastolic diameter (mm.)		
Range	6 1 – 15 0	12 0 – 23 3
Mean ± SE	11 4 ± 0 4	18 7 ± 0 3

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Acyanotic congenital heart disease

Left to right shunt

Shunts at atrial level Echocardiography is of most value in the diagnosis of shunts at the atrial level Popp and co workers[19] studied echoes from the interventricular septum and described a technique for determination of right and left ventricular dimensions. They noted that patients with atrial septal defects and large left to right shunts (QP/QS > 2/1) had an increased right ventricular internal dimension (RVD) and an abnormal pattern of ventricular septal movement (Fig 2) In normal subjects the septum and posterior left ventricular wall move toward each other during ventricular systole the septum moves posteriorly and the posterior left ventricular wall moves anteriorly In patients with atrial septal defects septal motion was paradoxical In type A

Ultrasound in the diagnosis of congenital heart disease

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The widespread use of ultrasound is a relatively recent development In 1950 Von Keidel[1] attempted to study the heart ultrasonically In 1954, Edler and Hertz[2] recorded movements from the posterior ventricular wall and the anterior mitral leaflet Edler and Gustafson s[3] observation that the severity of mitral stenosis could be predicted by ultrasound was confirmed by Joyner and others[4 6] in the early mid 1960 s Since 1967, however there has been a virtual explosion of information and developments in the field of ultrasound and the list of applications continues to grow [7] The echocardiogram is now routinely used for widely disparate anatomic and physiologic purposes such as detecting pericardial effusion [8] assessing the degree of obstruction in idiopathic hypertrophic subaortic stenosis [9] and in estimating left ventricular systolic and diastolic volumes [10 12] ejection fraction [10] and velocity of circumferential fiber shortening [13 14] The purpose of this paper is to review the virtues and limitations of ultrasound in the diagnosis of congenital heart disease in both adult and pediatric age groups

The principles and techniques of echocardiography have already been well presented [15 16] In the child the relatively thin chest wall and absence of obstructive lung disease often makes examination technically easier Study of the neonate is further simplified by the cartilaginous noncalcified sternum which permits readier penetration of the ultrasonic beam to the tricuspid valve and right ventricle The proximity of the heart to the skin surface in neonates requires adjustment in gain setting, as the mitral echoes are located at a depth of only 3 to 4 cm compared to normal adults in whom the depth of the mitral echo is 6 to 8 cm from the transducer Similarly, for identification of the neonatal septum and tricuspid valve the gain and depth control are appropriately adjusted for near echoes [17] Normal echocardiographic measurements for newborns have been established by Hagan and colleagues [18] and are presented in Tables I through III

In both children and adults the transducer is placed at the third fourth, or fifth left interspace near the sternal edge The placement site often depends on the size of the patient and the relative size and position of the heart Easily recognized echoes from the anterior mitral leaflet are first identified and the transducer is then swept in an arc superiorly and medially to the base (Fig 1) and inferiorly and laterally to the ventricular apex

Table I Echocardiographic criteria for normal newborn infants*

	Velocity (mm./sec.)	*Excursion (mm.)*
Tricuspid		
Range	60 - 116	7 0 - 14 0
Mean ± S E.	93 ± 2	9 3 ± 0 2
Mitral		
Range	60 - 130	6 0 - 12 0
Mean ± S E	80 ± 1	8 1 ± 0 1

From Hagan A D Deely W J Sahn D and Friedman W F Echocardiographic criteria for normal newborn infants Circulation 48 1221 1973

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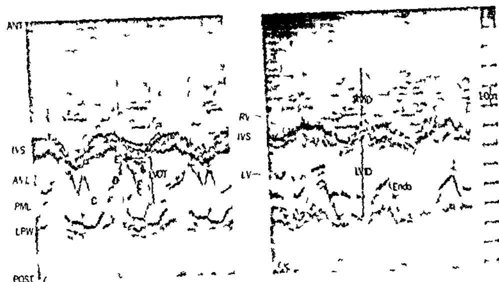


Fig 3 Echocardiogram from a patient with an ostium primum atrial septal defect The horizontal arrow represents prolonged mitral septal apposition in early diastole The distance between the endocardial surface of the septum and the closed position of the mitral valve during early systole (22 mm) represents a minimally reduced left ventricular outflow tract (LVOT) commonly seen in primum defects Increased right ventricular internal dimension (RVID) and abnormal (type A) septal motion are shown Abbreviations ANT anterior POST posterior RV right ventricle IVS septum AML anterior mitral leaflet PML posterior mitral leaflet LPW left ventricular posterior wall LV left ventricle LVID left ventricular internal dimension and Endo endocardium

or stopped Recently the need for caution in the interpretation of septal motion has been emphasized The upper portion of the interventricular septum moves anteriorly during systole in normal subjects [19,25] Only below the level of the mitral leaflets would systolic anterior septal motion be considered abnormal [25] Such clearly abnormal septal motion may be absent in more than one third of the patients with right ventricular volume overload [25]

Gramiak and Nanda[26] studied five adult patients with ostium primum septal defects. In addition to paradoxical septal motion they noted a narrow left ventricular outflow tract (measured from the left side of the ventricular septum to the mitral valve echo at the onset of systole) and prolonged mitral septal apposition in diastole corresponding to the angiographic goose neck deformity (Fig 3) In contrast, a group of patients with secundum type defects showed normal left ventricular outflow dimensions and absent or brief mitral septal apposition Lundström and Edler[27] described three patients with primum defects whose anterior mitral leaflet echoes consisted of two parallel echoes separated by a distance of 7 to 9 mm correlating angiographically and surgically with the two parts of the cleft anterior mitral leaflet Atrial-septal defect and mitral regurgitation may co exist in the partial form of endocardial cushion defect Significant mitral regurgitation leads to volume overload of both ventricles and may result in normal ventricular septal movement.[21] In this setting the diagnosis of atrial septal defect may be suspected from the increased right ventricular dimension index and the increased mobility of the tricuspid valve while partial endocardial cushion defect with mitral regurgitation may be suspected from the combination of increased mobility of the mitral valve and narrowing of the left ventricular outflow tract Williams and Rudd[28] studied varying types of endocardial cushion defect from simple ostium primum to complete common A V canal. They did not detect the mitral valve excursion in its usual location but instead mitral valve echoes were found by tracing rightward and anteriorly to the left ventricular outflow tract [28] Because the anterior mitral valve is tethered to the interventricular septum by abnormal chordae and is generally separated by a cleft into a superior and inferior portion its position and motion are abnormal Thus the superior segment of the anterior leaflet of the mitral valve is lifted upward into the left ventricular outflow tract,

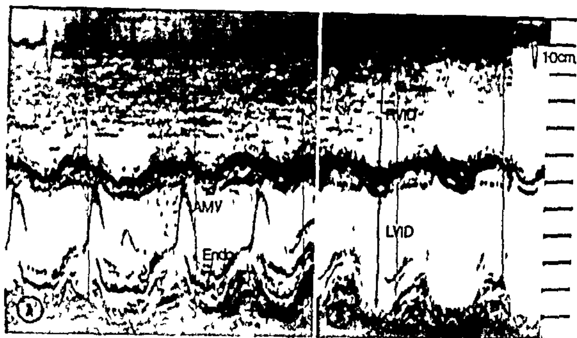


Fig 2 Echocardiogram from a patient with an ostium secundum atrial septal defect and atrial fibrillation The right ventricular internal dimension (RVID) is increased and measures 3 8 cm The septal motion is abnormal (type A) and is consistent with a volume overload of the right ventricle Both the left ventricle posterior wall (Endo and Epi) and the septum (SEP) move in the same direction during systole Abbreviations AMV anterior mitral valve leaflet RVID right ventricular diameter LVID left ventricular diameter Endo endocardium and Epi epicardium

movement the septum moved in an anterior direction during ventricular contraction and in type B movement the septal motion was flattened *during ventricular systole*

Diamond and co workers[20] attempted to quantify the left to right shunt in adults with atrial septal defect Thirty nine patients with both primum and secundum defect were catheterized and studied echocardiographically Two specific echo features were evaluated, namely the right ventricular dimension index (RVD) (or the right ventricular dimension divided by the body surface area expressed in centimeters per square *meter), and the motion pattern of the inter* ventricular septum In all patients studied the right ventricular dimension index was increased Moreover, in patients with a normal pulmonary vascular resistance (PVR) there was a direct linear relationship between the right ventricular dimension index and the pulmonic/systemic flow ratio, even when the shunt flow was small *(QP/QS* < 2/1) As resistance rises QP/QS may fall however, the right ventricular dimension actually increased Diamond found that thirty seven out of thirty nine patients with atrial septal defects had abnormal ventricular septal movement In thirty five of the thirty seven abnormal subjects, the interventricular septum moved paradoxically, while in the remaining two subjects, the septal echoes were flattened during ventricular systole The two patients with normal ventricular septal movement had very high PVR and balanced shunts *Although the right ventric*ular dimension index was occasionally increased in patients with pressure overload of the right ventricle such as pulmonic stenosis, abnormal septal motion was seen only in the volume overloaded right ventricle

Isolated partial anomalous pulmonary venous connection[21] and tricuspid regurgitation can both result in an increased right ventricular dimension index and abnormal septal motion Thus *both can be echocardiographically* indistinguishable from atrial septal defects Total anomalous pulmonary venous connection might be distinguished by the small left atrial size[22] Following surgical correction of atrial septal defects septal movement usually returns to normal within weeks to months especially if the right ventricular *dimension index is reduced* by one third or more of its preoperative value[23]

The mechanism of the septal abnormality has been studied in dogs by Dippel and Kerber[24] They found that paradoxical septal motion was produced by pumping as little as 400 c c per minute of blood from the left atrium to the right atrium *(QP/QS = 1 3/1) and septal motion re*turned to normal when the shunt was decreased

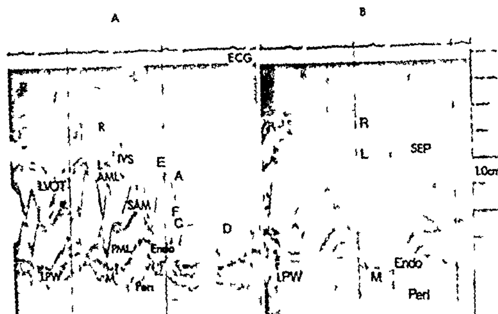


Fig 4 Echocardiogram in a 12 year old patient with the familial form of IHSS Panels *A* and *B* show the markedly thickened septum measuring 1 3 cm with the left ventricular posterior wall measuring 0 7 cm (septal/posterior wall ratio = 1 9) Panel *A* shows a left ventricular outflow tract (LVOT) of 1 9 cm. and marked systolic anterior motion (SAM) of the anterior leaflet of the mitral leaflet (AML) The diastolic closure slope (E F slope) is reduced measuring 38 mm per second Abbreviations R right side L left side IVS interventricular septum SEP septum PML posterior mitral leaflet Endo endocardium M myocardium Peri pericardium and LPW left ventricular posterior wall.

area of the left ventricular outflow tract below the aortic valve [40] Additional features include abrupt premature closing and reopening of the aortic valve shortly after the onset of ventricular ejection [41,42] Other nonspecific findings include aortic valve fluttering [41] systolic anterior bulge of the anterior mitral leaflet and a high intensity thin echo in the left ventricular outflow tract which was thought to represent the subaortic diaphragm [42]

IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS (IHSS) IHSS is chiefly characterized by asymmetrical septal hypertrophy [43,44] Echocardiographic features include a septal posterior wall ratio greater than 1 3 and usually greater than 1 6 [43,44] systolic anterior movement of the mitral valve [45-47] reduced diastolic closure slope (E F slope) of the mitral valve [38,45] (Fig 4) and mid systolic closure of the aortic valve followed by a reopening movement [15] Using an obstruction index (calculated by dividing the duration of outflow narrowing by the mean septal anterior mitral leaflet distance) Henry and colleagues[9] found a good correlation with the simultaneously measured peak left ventricular outflow pressure gradient Echocardiography has also been found to be of value in assessing the response to medical and surgical treatment [47] In patients with IHSS and co existing fixed left ventricular outflow obstruction echocardiography may be of help in identifying the combined anatomic abnormalities [48]

SINUS OF VALSALVA ANEURYSM In a recent case report of a right sinus of Valsalva aneurysm, echocardiography demonstrated an abnormal structure extending from the aortic root into the left ventricular chamber adjacent to the inter ventricular septum [49] The abnormal echo showed diastolic motion away from the septum and systolic motion toward the septum which appeared to correlate with the cineangiographic filling of the aneurysm during diastole and emptying during systole [49] Additional findings included exaggerated anterior systolic motion of the right aortic cusp and eccentricity of the aortic valve leaflets [49] an echocardiographic pattern not dissimilar to that seen in congenital bicuspid aortic valve [33]

CONGENITAL OBSTRUCTION TO LEFT ATRIAL FLOW MITRAL STENOSIS Congenital mitral

producing a characteristic echocardiographic finding as well as the typical angiographic goose neck deformity In endocardial cushion defects, *two additional abnormal patterns of* valve motion were observed In transitional cushion defects the anterior leaflet of the tricuspid valve approached the anterior mitral valve in the plane of the interventricular septum during systole *During diastole the* tricuspid valve had an excessive anterior motion in the right ventricle

In complete cushion defect a single A V valve leaflet demonstrated an abnormally large excursion from a systolic posterior position in the left *ventricle to a diastolic anterior* position touching the right heart border This pattern could not be readily distinguished from tricuspid atresia or single ventricle with a common A V valve

In addition to the endocardial cushion defect, *combined atrial septal defect and mitral* regurgitation may be due to the unexplained association between mitral valve prolapse and secondary atrial septal defect [29] Here the characteristic echo features of systolic mitral prolapse are seen *in association with right ventricular volume* overload

Shunts at ventricular level Uncomplicated ventricular septal defect has no distinguishing echocardiographic features If shunt flow is large *left atrial and ventricular dimensions are in*creased When the ventricular septal defect is associated with a large left to right shunt and a pressure overloaded right ventricle the right ventricular dimension index may be increased but septal motion is *normal* [20] Carter and Bowman[30] have shown a linear relationship between the echo determined left atrial dimension and the volume of left to right shunt in isolated VSD Patients with shunt flows equal to or greater than 2/1 had left atrial dimension indices in excess of 3 cm per square meter [30]

In patients with *small* membranous ventricular septal defects, septal aneurysm formation may be the prelude to spontaneous closure [31] *In a* recent study of an aneurysm of the membranous interventricular septum abnormal echoes with wide excursion and protrusion into the right ventricular outflow tract were noted.[32] In addition these echoes appeared to originate off the base of the interventricular septum and were closely linked to systolic motion of the tricuspid valve [32]

Shunts at great vessel level Uncomplicated patent ductus arteriosus or aortico pulmonary window have no distinguishing echocardiographic features *If there is torrential* flow through a great vessel shunt, increased left atrial and left ventricular size may be expected but, in general the echocardiogram is of little assistance in making this diagnosis

Absent shunt

Malformations originating in the left heart

AORTIC STENOSIS Obstruction to left ventricular outflow can occur at valvular subvalvular, or supravalvular levels

*VALVULAR AORTIC STENOSIS The most com*mon congenital defect resulting in aortic stenosis is caused by a bicuspid aortic valve In 14 patients with proven bicuspid aortic valve marked eccentricity of the valve was found [33] In systole the cusps opened briskly to the periphery of the aortic lumen producing some degree of asymmetry [33] Significant aortic stenosis in childhood is seldom due to a trileaflet valve with failure of commissural separation and is occasionally due to a unicuspid valve [34] No echocardiographic features of these valves have been described It is known *that mobile but severely stenotic valves in child*hood may appear to have a normal systolic orifice [35] This may be due to doming of the valve with the transducer beam recording from a level below the effective orifice In contrast in adults *even mild aortic stenosis reduces* the apparent echocardiographic aortic valve orifice dimension [36] When the aortic valve calcifies the echocardiographic patterns include a loss of the usual cusp architecture and thick multilayered complexes within the aortic root [37,38] Occasionally, no valvular motion is seen in systole and the thick multilayered complex continues throughout systole and diastole [38] Calcification is age dependent and therefore it is unlikely to occur in the pediatric age group [34]

SUBVALVULAR AORTIC STENOSIS Subvalvular aortic stenosis may be fixed (discrete anatomic stenosis) or dynamic (muscular or idiopathic hy*pertrophic subaortic* stenosis)

DISCRETE SUBAORTIC STENOSIS Two general forms of discrete subaortic stenosis exist [39] *In the* first type a thin subvalvular membrane or diaphragm is present below the aortic valve The membrane is usually attached to the anterior mitral valve leaflet In the second type a long narrow *fibromuscular chamber* is present The most consistent echocardiographic feature of discrete subvalvular *aortic stenosis is a narrowed*

COR TRIATRIATUM Cor triatriatum is characterized by connection of the pulmonary veins into a proximal left atrial chamber that lies above the true left atrium[34] The fibrous or fibromuscular diaphragm that partitions the left atrium possesses one or more openings the size of which determines the degree of left atrial obstruction[34] The mitral valve is normal Echocardiographic studies of cor triatriatum have revealed the expected normal mitral valve[56,58] and in two instances[58,59] an abnormal band of echoes in the left atrial chamber In one patient a postoperative study showed an echo free left atrium following removal of the intra atrial partition[58]

Malformations originating in the right heart PULMONIC STENOSIS WITH INTACT VENTRICULAR SEPTUM The pulmonary valve shows echocardiographic opening and closing movements similar to those of the aortic valve[59] The pulmonary valve may be distinguished echocardiographically from the aortic valve because its normal position lies anterior lateral and superior to the aortic valve[59] Moreover only the left or posterior pulmonary cusp is usually seen while two aortic cusps are visualized in most instances

Weyman and associates[60] studied the echocardiograms of 14 patients with isolated pulmonic stenosis They found that right atrial contraction normally imparted a slight degree of posterior motion to the posterior pulmonic leaflet in presystole (average 3 mm) but the leaflet returned to a closed position prior to ventricular systole (Fig 6) In patients with pulmonic valvular gradients of 50 to 142 mm Hg the leaflet motion increased (average 10 mm) and in those patients whose gradient exceeded 65 mm Hg the pulmonic leaflet never returned to the closed position prior to ventricular systole (Fig 6) The authors speculate that this exaggerated posterior pulmonic leaflet movement following atrial systole is due to the increased right ventricular end diastolic pressure transmitted to the mobile pulmonic valve[60]

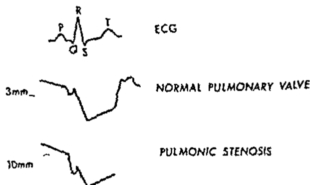


Fig 6 Schematic representation of patterns of motion of the pulmonic valve In normal subjects atrial contraction produces a slight degree of posterior motion in presystole averaging 3 mm In patients with pulmonic stenosis there is increased posterior atrial motion (10 mm or more) and the pulmonic valve leaflet does not return to the closed position prior to ventricular systole

Cyanotic congenital heart disease

Normal or decreased pulmonary arterial flow

Dominant left ventricle TRICUSPID ATRESIA According to Edwards and co workers[61,62] the anatomic classification of tricuspid atresia relates to three variables transposition of the great arteries the absence or presence and degree of pulmonic stenosis, and the size of the ventricular septal defect The most common variety of tricuspid atresia is associated with normally related great arteries small VSD, hypoplastic right ventricle and pulmonic stenosis (Fig 7) In newborns the echocardiographic criteria are absent tricuspid valve echoes and a rudimentary right ventricular cavity[63] As mentioned above the tricuspid valve in the neonate is readily accessible to the transducer beam[17] In older children and adults however, the tricuspid valve echoes are normally difficult to visualize in the absence of right ventricular dilation so these criteria are less reliable

The single atrioventricular valve leaflet may move abnormally far anteriorly (Fig 7) in contrast to that of a normal anterior mitral leaflet[64,65] Septal echoes are not always recorded.[65] The small right ventricle contrasts with the large left ventricle[63] A small right ventricular cavity may also associate with pulmonary atresia with intact ventricular septum although a well developed right ventricular cavity may be present especially when the tricuspid valve is incompetent[66] echocardiographically the size of the right ventricle is variable and tricuspid valve motion may be recordable In tricuspid atresia without pulmonic stenosis transposition of the great arteries is more likely to co exist The right ventricle is well developed because a large VSD is usually present Echocardiographically one would expect features of transposition (see below) and a single A V valve

Ebstein s anomaly of the tricuspid valve The anatomic features of Ebstein s anomaly consist of

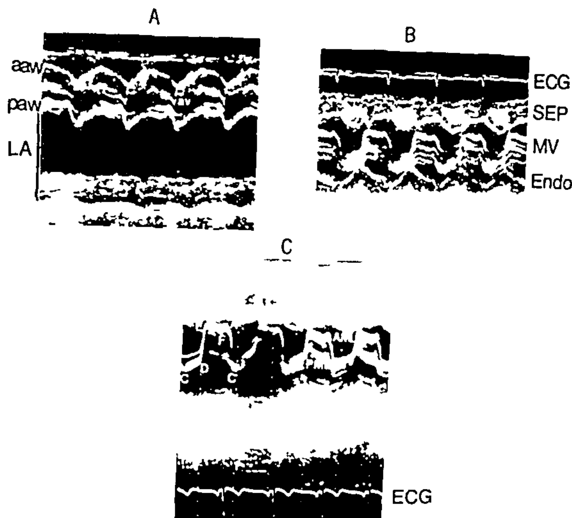


Fig 5 Echocardiograms of a 16 year old patient with congenital mitral stenosis and suspected parachute deformity on angiography Panel *A* shows normal aortic root and aortic valve with an enlarged left atrium behind the aortic root measuring 5 5 cm Panel *B* shows normal left ventricular cavity with a mitral valve showing slow diastolic closure slope of 15 mm per second and a diminished A wave Panel *C*, shows the posterior mitral leaflet (PML) moving in the same direction as the anterior leaflet (AML) The amplitude of excursion of the anterior mitral leaflet is normal measuring 29 mm Abbreviations AAW anterior aortic wall PAW posterior aortic wall LA left atrium SEP septum MV mitral valve and Endo endocardium

stenosis is rare and seldom exists as an isolated lesion Several anatomic varieties of congenital mitral stenosis have been described in patients with functionally adequate left ventricles One variety is the parachute mitral valve in which leaflets cannot separate in diastole because short thickened chordae insert into a single papillary muscle [51,52] In the second type of congenital mitral stenosis, the mitral leaflets may be thickened, with rudimentary commissures, *shortened*, thickened chordae and fibrosed papillary muscles [53,54] The valve is transformed into a funnel shaped structure

Lundstrom[55] studied seven patients with the second variety of congenital mitral stenosis and co existing cardiovascular malformations echocardiographically He consistently found a reduced diastolic closure slope (E F slope) of the anterior mitral leaflet and low to normal total amplitude of motion of the anterior leaflet in five patients In only two patients was the total amplitude of anterior mitral *leaflet movement* abnormal and this corresponded to restricted mobility of the valve from short fused chordae demonstrated either at surgery or at autopsy The severity of the stenosis was directly related to the degree of reduction in the E F slope (Fig 5) *corresponding to* the echo features of acquired mitral stenosis in adults In children Lundstrom[55] found the normal E F slope to be 90 mm per second Children with slopes of greater than 30 mm per second had slight mitral stenosis at surgery and those with slopes below 20 to 25 mm per second had severe stenosis [55]

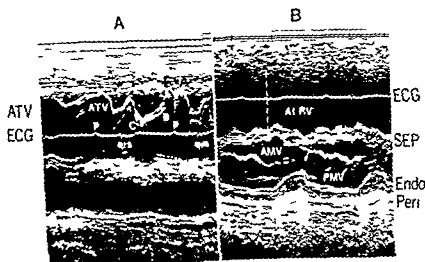


Fig 9 Echocardiogram from a 14 year old patient with Ebstein s anomaly of the tricuspid valve A shows three distinct movements of the tricuspid valve Following the P wave the valve reopens at point A and then assumes a semiclosed position. The valve reopens immediately after the QRS complex and then delayed closure occurs at point C. Abbreviations ATV anterior tricuspid valve B shows the large atrialized right ventricle (AtRV) and an abnormal flat (type B) septal motion. Abbreviations SEP septum AMV anterior mitral valve PMV posterior mitral valve Endo endocardium and Peri, pericardium

compared to mitral valve closure [68-70] That the delayed tricuspid valve closure is not merely a reflection of the right bundle branch block (RBBB) commonly seen in Ebstein s anomaly is suggested by Tajik and co workers [71] They found delayed tricuspid closure in a patient with Ebstein s anomaly and type B Wolff Parkinson White syndrome. Pre excitation leads to earlier excitation of the right ventricle and should result in earlier closure of the tricuspid valve In their patient with pre excitation and Ebstein s anomaly delayed tricuspid closure was a specific feature of the abnormally positioned tricuspid valve and was independent of RBBB The degree of motion of the anterior leaflet of the tricuspid valve depends upon anatomic variations. If the anterior leaflet is a large sail like structure that retains part of its attachment to the true annulus, then the characteristic echocardiographic feature of excessive amplitude of movement of the tricuspid leaflet will be recorded (Fig 8) [72] However if the leaflet is tethered to the atrialized portion of the right ventricle normal or even diminished amplitude of the tricuspid leaflet will occur The anterior leaflet of the tricuspid valve may be functionally competent incompetent or stenosed, and thus variable diastolic closure slopes may be recorded by ultrasound.[72] Abnormal diastolic mitral valve motion has been reported in Ebstein s anomaly of the tricuspid valve[71] and Fig 9 is an example of abnormal diastolic motion of the tricuspid valve

Dominant right ventricle

ABSENT PULMONARY HYPERTENSION TETRALOGY OF FALLOT In classic cyanotic Fallot s tetralogy a large ventricular septal defect is situated in a basal position beneath the mouth of the aorta [34] The aorta may emerge chiefly from the right ventricle chiefly from the left ventricle or may straddle the ventricular septal defect more or less equally [34] The dextro position may be considerable but the aortic valve consistently maintains anatomic continuity with elements of the anterior mitral leaflet. Varying degrees of infundibular and/or valvular pulmonary stenosis are present Chung and associates[73] described echocardiographic studies of 17 patients with the diagnosis of tetralogy of Fallot As evidence of an overriding aorta they found discontinuity between the ventricular septum and anterior aortic wall in 15 of these patients (Fig 10) The normal anterior mitral leaflet posterior aortic wall continuity was preserved in 10 patients but in 7 patients the mitral valve closed in a position deep to the posterior aortic wall (5 to 20 mm)

RIGHT VENTRICULAR ORIGIN OF BOTH GREAT VESSELS WITH PULMONIC STENOSIS (DOUBLE OUTLET RIGHT VENTRICLE) In double outlet right ventricle the pulmonary trunk arises normally, but the aorta arises wholly from the right ventri

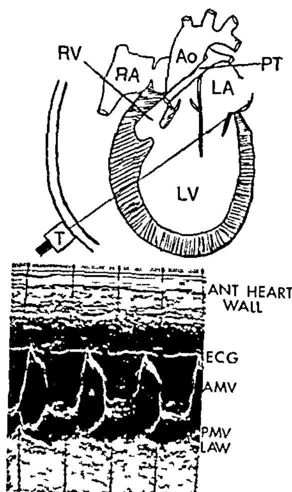


Fig 7 *Top* schematic representation of the most common type of tricuspid atresia with normally related great vessels and pulmonic stenosis The ventricular septum has a narrow slit like opening that represents the only communication be tween the left ventricle and the rudimentary right ventricle Abbreviations T transducer RV right ventricle RA right atrium Ao aorta LA left atrium PT pulmonary trunk and LV left ventricle *Bottom,* echogram of such a patient with tricuspid atresia showing marked anterior movement of the mitral valve (AMV) No definite septal echoes or tricuspid valve motion could be demonstrated. Abbreviations PMV posterior mitral valve echo and LAW left atrial wall

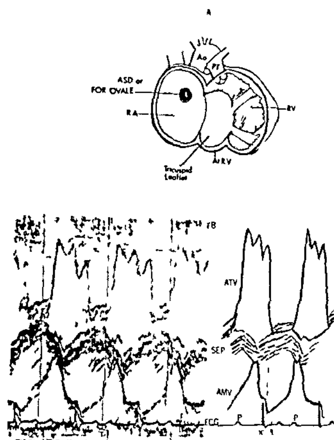


Fig 8 *A* schematic illustration of the essential anatomic and mechanical abnormality in Ebstein s anomaly The large an terior tricuspid valve leaflet is displaced downward and divides the right atrium into a true right atrium (RA) and an atrialized right ventricle (At RV) Abbreviations ASD atrial septal defect for ovale foramen ovale RV right ventricle Ao aorta and PT pulmonary trunk *B* echocar diogram of a 15 year old patient with Ebstein s anomaly of the tricuspid valve The increased anterior movement of the tricuspid valve (ATV) as compared to the mitral valve (AMV) is shown Tricuspid valve closure (tc) follows mitral valve closure (mc) by 40 milliseconds as shown in the schematic il lustration on the right Tricuspid valve motion has been redrawn for clarification There are three distinct tricuspid valve opening movements during diastole Abbreviations SEP septum

displacement of fused malformed portions of tri cuspid valve tissue into the right ventricular cavity (Fig 8)[62] The chordae tendineae are at tached directly to the endocardium, or the valvu lar tissue itself may be adherent to the endocar dium The anterior tricuspid leaflet is usually the largest and least affected, while the septal and posterior leaflets show the most deformity[34 62 67] The portion of the right ventricle underlying the adherent tricuspid valve is thin and functions mechanically as part of the right atrium, although it generates a right ventricular in tracavitary electrogram

Abnormal function of the right heart in Eb stein s anomaly is related to (1) the malformed tricuspid valve (2) the ' atrialized portion of the right ventricle and (3) the reduced capacity of the pumping portion of the right ventricle[34] These patients have dilated right atria, and most have a secundum ASD or incompetent foramen ovale with right to left shunts

Echocardiographic features in Ebstein's anomaly include (1) delayed tricuspid closure compared to mitral closure[68 70] (2) increased amplitude of tricuspid valve motion as compared to mitral valve motion (Fig 8),[69] (3) decreased tri cuspid diastolic closure slopes (E F slope)[68] (4) di lated right atrium[69] and (5) abnormal inter ventricular septal motion[69 71]

The most consistent echocardiographic feature appears to be delayed tricuspid valve closure as

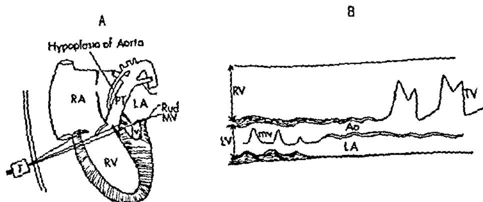


Fig 11 *A* schematic illustration of the essential anatomic and circulatory derangements in hypoplastic left ventricle The aorta is hypoplastic the mitral valve is rudimentary and the left ventricle is hypoplastic and non functional *B*, echocardiographic features may include absence of normal mitral valve echo small aortic root, and a small posterior left ventricle in the presence of a large anterior right ventricle Abbreviations T transducer RA right atrium RV right ventricle PT pulmonary trunk LA left atrium Rud MV rudimentary mitral valve LV left ventricle Ao aorta and TV tricuspid valve

the mitral annulus [77] In both patients there was anterior systolic movement and posterior diastolic movement of a structure that was clearly separated from the posterior heart wall and interventricular septum Absence of mitral leaflets were confirmed at autopsy

In patients with tricuspid atresia and transposition of the great vessels echocardiographic features may be indistinguishable from the hypoplastic left heart syndrome and single ventricle with common A V valve

Increased pulmonary arterial flow

Single ventricle. Single ventricle refers to the anatomic condition in which there are two atria but only one ventricular chamber an anatomic left ventricle which receives both the mitral and tricuspid valves [78] This form of single ventricle exists with a rudimentary outflow chamber representing the infundibulum of the right ventricle [79] The great arteries are almost always transposed D transposition [80] Occasionally a common atrioventricular valve is present instead of the usual separate mitral and tricuspid valves The majority of patients with a single ventricle studied echocardiographically by Meyer and Kaplan[63] demonstrated two atrioventricular valves (Fig 12) However in Chesler and coworkers[63] study a common A V leaflet with excessive motion was demonstrated. Meyer and Kaplan[63] believe the most specific echocardiographic features of a single ventricle to be an absent ventricular septum The entities most often confused with single ventricle are common ventricle" i.e absence of the ventricular septum and congenitally corrected transposition (L transposition) of the great vessels [63] In the latter the inverted ventricles lie side by side and the septum becomes perpendicular to the anterior chest wall Thus the transducer beam parallels the septum, and fails to record septal echoes

Complete transposition of the great arteries (D transposition) The term transposition refers in part to the anteroposterior relationships of the great arteries The aorta is located anterior to the pulmonary trunk and in addition takes origin from the anatomic *right* ventricle while the pulmonary trunk originates from the posterior anatomic *left* ventricle Complete transposition is one of the most common causes of congestive heart failure in cyanotic infants

An attempt to recognize complete transposition echocardiographically was first described by Gramiak and colleagues [81] Using a technique previously employed to detect the pulmonary valve [59] they found that in patients with complete transposition medial transducer angulation from a left parasternal position demonstrated an anteriorly situated outflow vessel and lateral transducer angulation from the same position showed a posteriorly placed outflow vessel In normal subjects lateral transducer angulation located the anterior pulmonary vessel and medial angulation detects the posterior aorta A major limitation of this method is that correct interpretation of the echocardiogram is based solely on knowing the angulation of the transducer during the recording If the transducer

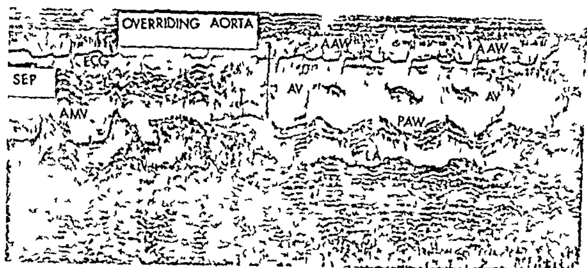


Fig 10 Echocardiogram from a 7 year old patient with tetralogy of Fallot. As the ultrasonic beam scans from the left ventricle to the base of the heart the dilated aorta (distance between AAW and PAW) overrides the interventricular septum (SEP) The noncoronary cusp of the aortic valve (AV) is clearly visualized. Abbreviations AMV anterior mitral valve AAW anterior aortic wall PAW posterior aortic wall and LA left atrium

cle [34] A ventricular septal defect provides the left ventricle with its only outlet. In double outlet right ventricle pulmonic stenosis may or may not co exist The echocardiographic features of typical double outlet right ventricle have been described by Chesler and co workers [74] In five patients the end systolic (closed) position of the anterior mitral leaflet was posterior to the posterior aortic root margin, corresponding to the anatomic separation of these structures While the authors felt that the echo evidence of mitral aortic discontinuity was quite specific for double outlet right ventricle echocardiographic discontinuity has been noted in some patients with tetralogy of Fallot [73] The practical consideration is obvious Failure to correctly distinguish double outlet right ventricle from tetralogy of Fallot leads to operative disaster if the ventricular septal defect is closed The echocardiogram lacks specificity as the sole arbiter in making this distinction and preoperative angiographic study remains essential

TRUNCUS ARTERIOSUS Truncus arteriosus is an uncommon congenital anomaly wherein a single great vessel leaves the base of the heart through a single semilunar valve The pulmonary valve is absent The truncus arteriosus receives blood from both ventricles through a ventricular septal defect Four anatomic types have been classified according to the point of origin of the pulmonary arteries with respect to the truncus vessel [34]

Chung and co workers [75] performed echocardiograms on five children with catheterization proved truncus arteriosus Using their previously described technique for the detection of the pulmonic valve, [69] they were unable to locate pulmonic valve echoes in these patients Moreover, the ultrasonic studies showed a large aortic root and discontinuity between the ventricular septum and the anterior aortic wall The authors cautioned however, that the echoes from the pulmonic valve may be found in only 40 to 92 per cent of normal children, and that absence of this structure on the echocardiogram is not, therefore, diagnostic of truncus arteriosus Furthermore some echocardiographic features of truncus arteriosus could be confused with severe tetralogy of Fallot or pulmonary atresia with ventricular septal defect

Pulmonary hypertension present

Hypoplastic left heart syndrome Hypoplasia of the left ventricle in its most severe form consists of a slit like ventricular cavity, atresia of aortic and/or mitral valve and severe hypoplasia of the ascending aorta [76] Echocardiographic features characteristic of this complex include absence or gross distortion of the mitral valve echo small to absent aortic root, and a small posterior left ventricular chamber in the presence of an enlarged right ventricle (Fig 11) [17,63] In the series reported by Meyer and Kaplan, [63] the mean left ventricular chamber measured less than 0 9 cm and the mean right ventricular chamber measured 2 5 cm

In two patients with mitral atresia studied by Lundström [56] echoes obtained from the region where the mitral valve was expected to be localized, resembled the echo patterns described from

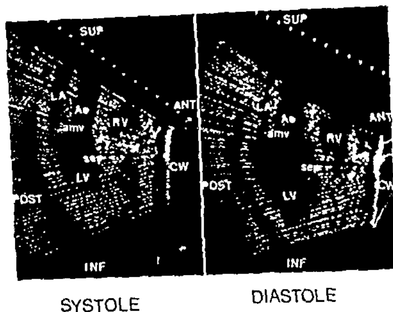


Fig 13 Long axis cross section during systole and diastole in a normal 14 year old boy The appearance is similar to that seen on a lateral or left anterior oblique angiocardiogram The upper interventricular septum (SEP) is seen crossing from the anterior heart wall to the anterior wall of the aortic root resulting in an oval cross section of the right ventricular outflow tract (RV) Abbreviations SUP superior ANT anterior CW chest wall Ao aorta LA left atrium AMV anterior mitral valve LV left ventricle INF inferior and POST posterior

Newer developments in cardiac ultrasound in the diagnosis of congenital heart disease

Cardiac ultrasonography Compound B stop action scanning or cross sectional imaging of the heart records a two dimensional image of a section through the heart. The completed image is formed by a composite of multiple sequential B scan recordings Systolic or diastolic images can be obtained by the use of a stop action device triggered by the QRS complex of the patient s electrocardiogram. The technique of recording compound B scans has been described by King [83] Compound B ultrasonography surpasses conventional echocardiography in its ability to provide accurate anatomic detail of the chambers of the heart and outflow vessels as well as its ability to record both the major and minor axes of the left ventricle Disadvantages include the inability to record the right atrium and part of the right ventricle In addition inability to record accurately over the plane of the septum may prevent filling in" of the apex of the left ventricle The technique is time consuming and cumbersome and rapid cardiac rates may prevent the stop action of the gating circuit from functioning effectively Valuable information regarding the mobility of the valves, septum and left ventricular wall may be lost with this technique as compared to conventional echocardiography

Preliminary studies by others[83 89] have confirmed the feasibility of employing the technique of compound B ultrasonography in the diagnosis of various cardiac disorders Its usefulness in the determination of left ventricular volume[84] and the detection of left ventricular wall abnormalities[89] has been demonstrated. Moreover its diagnostic value in transposition of the great arteries[86] and ventricular septal defect[87] appears to exceed that of conventional echocardiography

Compound B ultrasonography accurately *depicts the normal relationship of the great arteries* The normal crossed or spiral relationship of the right and left ventricular outflow tracts and great arteries was present when the long axis cross section showed the upper ventricular septum crossing from the upper anterior ventricular wall to the anterior wall of the aortic root (Fig 13) By contrast patients with transposition of the great arteries demonstrated both ventricular outflow tracts and arterial trunks in parallel alignment (Fig 14 *A*) In addition the anterior chamber and aorta are uninterrupted by a crossing interventricular septum In the transverse *cross section* the anterior artery (aorta) was

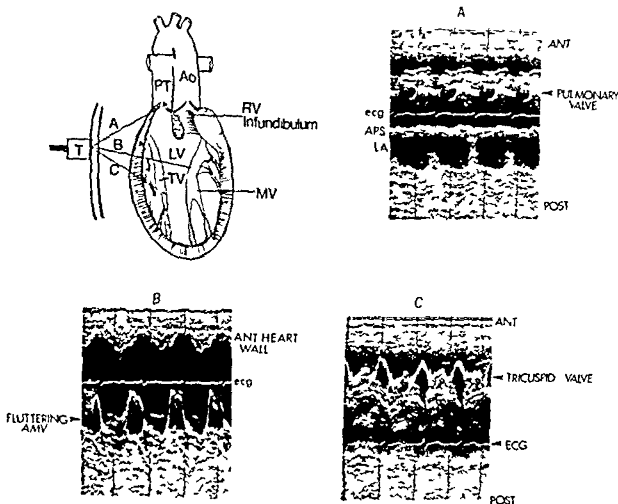


Fig 12 Schematic illustration of single ventricle (upper left hand quadrant) The ventricular portion of the heart consists of a morphologic left ventricle (LV) with a small outlet chamber that represents the infundibular portion of the right ventricle (RV infundibulum) The mitral (MV) and tricuspid valve (TV) are separately arranged and transposition of the great vessels is present Abbreviations PT pulmonary trunk and Ao aorta Panels A B and C refer to the three transducer positions demonstrated in the upper left panel and are representative echocardiograms of an 18 year old patient with single ventricle transposition of the great arteries and no pulmonic stenosis (pulmonary hypertension and insufficiency) Panel *A* shows enlarged pulmonary trunk pulmonary valves atriopulmonic sulcus (APS) and left atrium (LA) Panel *B* shows excessive posterior systolic movement of the anterior heart wall and significant anterior movement of the anterior mitral valve leaflet (AMV) Septal echoes could not be recorded. The AMV demonstrates evidence of flutter in diastole as a result of insufficiency of the pulmonary valve Panel *C* shows tricuspid valve motion. Abbreviations *ANT* anterior and *POST* posterior

position is not known the anterior outflow vessel *looks exactly like the normal pulmonary artery* and the posterior vessel resembles the aorta

More recently Dillon and associates[82] studied 16 patients with D transposition of the great arteries They observed that the normal pulmonary valve was anterior superior, and to the left of the aortic valve The anterior wall of the aorta (which is also the posterior wall of the right ventricular outflow tract) dipped posteriorly as the pulmonary valve echo appeared. Posterior to the pulmonic valve was a thick band of echoes probably originating from the crista supraventricularis The lower portion of the pulmonic valve echo and the crista lay in a plane at the same depth as the center of the aorta and aortic valve echoes *Normally echoes from both semilunar valves could not be recorded simultaneously* In all 16 patients with D transposition however, superimposition of the great arteries was noted without an intervening crista The great arteries ran parallel to each other and the anterior artery did not dip posteriorly Finally in 14 of the 16 patients echoes from both semilunar valves could be recorded simultaneously The authors[82] felt that the echocardiographic findings of superimposition of the great arteries without intervening crista, together with simultaneous recording of the semilunar valves is diagnostic of D transposition of the great arteries

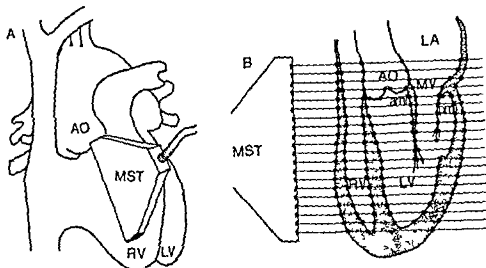


Fig 15 Schematic illustration of the multiscan transducer (MST) in an oblique position overlying the heart. Panel B shows the cardiac structure lying in the plane below the transducer Abbreviations AO aorta RV right ventricle LV left ventricle MV mitral valve AML, anterior mitral leaflet PML posterior mitral leaflet and LA left atrium

well described.[91-93] In a study of over 150 patients Kloster and associates[94] have utilized two standard transducer positions one producing an image of a sagittal cross section in the plane of the septum (Fig 15) and the other a horizontal section across the ventricles Initial success in recording anatomic relationships of the major vessels and chambers of the heart has been confirmed by several investigators[94-97] Comparisons of aortic dimensions in 23 patients have compared favorably with angiographic measurements

In addition preliminary studies on 14 patients studied by multiscan cardiac cross sections and angiography have yielded reliable and comparable results with regard to end diastolic volumes and localized areas of hypokinesia[95] Systolic volumes stroke volumes and left ventricular ejection fractions were underestimated with the multiscan method as compared to angiography[95] In addition to the two positions introduced by Kloster and co workers[94] Sahn and co workers[97] have utilized four views with this system long axis sagittal, coronal in the fourth left intercostal space sagittal along the right ventricular outflow tract and coronal of great vessel orientation in the second intercostal space. These workers have been successful in visualization of all cardiac chambers and valves[97]

This exciting new technique should prove to be a useful screening procedure in infants with congenital heart disease As the technique becomes more refined, it may allow accurate diagnosis of complex congenital heart disorders in its own right

Real time two dimensional echocardiography Griffith Henry and Epstein[98] have developed a small hand held scanner that can be angled rapidly through a 30 arc by a servo controlled DC motor Real time two dimensional images of the heart and great arteries are generated. This technique has been useful in the differential diagnosis of anomalies of the great arteries[99]

Summary

In addition to recording the motion of the mitral tricuspid aortic and pulmonic valves echocardiography can identify right and left ventricular cavities and the interventricular septum. Disorders such as atrial septal defect valvular and subvalvular aortic stenosis pulmonic stenosis Ebstein s anomaly of the tricuspid valve and the hypoplastic left heart syndrome can readily be evaluated by echocardiography In tetralogy of Fallot and truncus arteriosus discontinuity between the anterior aortic wall and septum with overriding aorta has been demonstrated Double-outlet right ventricle is associated with posterior aortic wall and mitral valve discontinuity In disorders such as single ventricle tricuspid atresia and endocardial cushion defect with common A

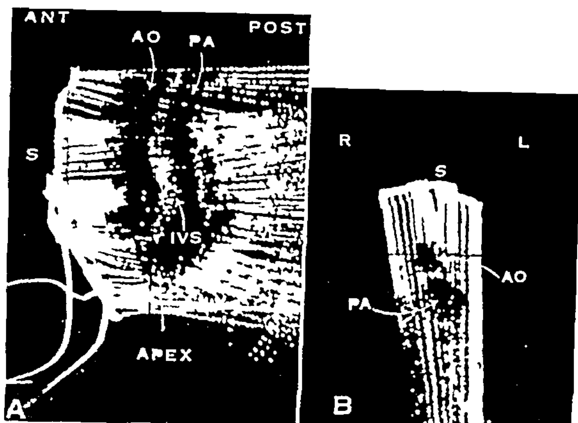


Fig 14 *A* long axis cross section of a patient with transposition of the great arteries The ventricular outflow tracts and arterial trunks appear parallel The interventricular septum (IVS) does not cross the upper portion of the anterior ventricle to produce an oval cross section of its outflow tract. *B* transverse cross section of the same patient along the left third intercostal space showing a slightly left anterior position of the anterior aorta Abbreviations ANT anterior POST posterior Ao aorta PA pulmonary artery S skin R right and L left. From King Steeg and Ellis Demonstration of transposition of the great arteries by cardiac ultrasonography Radiology 107 181 1973 By kind permission of Radiology and Dr King

displaced from its normal leftward position to a more anterior or rightward position of the posterior arterial trunk (Fig 14, *B*)

On the basis of these criteria King and associates[86] were able to diagnose correctly 14 out of 16 patients with transposition of the great arteries The technique is fraught with problems especially in small infants In addition, false positive results occur when the plane of cross sectional scanning does not pass through the left ventricular long axis because of marked right ventricular enlargement, as in atrial septal defects

King and associates[87] were able to demonstrate ventricular septal defects in 25 patients In many of these patients other defects were also present such as tetralogy of Fallot or transposition of the great arteries However compound B ultrasonography failed to demonstrate ventricular septal defects in 13 additional patients presumably because these defects were small

Cine ultrasound cardiography Gramiak Waag, and Simon[90] have recently reported a novel approach to the production of cross sectional motion picture studies of the heart using conventional ultrasonic techniques. The production of the cine ultrasonogram requires an M mode record performed with a single sector scanning motion of the ultrasonic beam By photographing the echocardiographic and electrocardiographic signal on 35 mm film at high recording speeds a permanent record of the sector scan is obtained. Narrow strips from the ultrasonic panorama at the inscription of each R wave are cut and mounted next to each other in continuity The resulting image is the equivalent of a cine frame Sampling is performed at other points in the cardiac cycle, and the mounting of sequential images of the same anatomic area produces a motion picture

Multiscan echocardiography Bom and coworkers[91] have recently introduced a multi element ultrasound transducer which employs a linear array of 20 elements to provide real time cross sectional images of the heart The technical and engineering aspects of this system have been

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V canal, echocardiographic demonstration of the absence of the interventricular septum has provided the clinician with valuable information

Newer techniques such as compound B ultrasonography, which produces a two dimensional cross sectional image of intracardiac structures and multiscan echocardiography will enhance the use of conventional echocardiography by providing a more accurate anatomic display of cardiac chambers and outflow vessels

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Cor pulmonale (pulmonary heart disease) present-day status

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Thirty years ago, reporting on data from our group at Bellevue Hospital, Richards[1] announced that there was a difference in the cardiac performance (referring here only to cardiac output) of patients with heart disease secondary to chronic obstructive pulmonary disease (COPD) (then designated as emphysema or as chronic emphysema and bronchitis) as compared to those with degenerative forms of cardiac disease. In January 1949, four years later, Dr. Harvey and I discovered, after studying a patient (who turned out to be characteristic of a larger group with COPD) for a second and then a third time following intensive cardiopulmonary treatment, that the pulmonary hypertension which was the keystone of cor pulmonale (today also called *pulmonary heart disease*) in contradistinction to a long held tenet was not fixed, immutable and hence eventually lethal, but rather, was a reversible hemodynamic complication in COPD.[2] Prior to World War II, the mechanism for pulmonary hypertension leading to cor pulmonale in chronic emphysema was stated unequivocally as being due to lung destruction, an anatomic unchangeable relentlessly hopeless process. Indeed, in the early forties and before the work just cited was done, patients with cor pulmonale and emphysema were kept in the same hopeless corner of our Bellevue wards as the advanced carcinomatoses and generally they all succumbed, quietly, in carbon dioxide narcosis and right heart failure.

Thus in the mid and late forties a new era began for the patients with cor pulmonale as the abnormal physiology responsible for right heart involvement became the focus of intensive research by our own and other groups. The pulmonary hypertension of COPD was found to be reversed or obliterated by improvement in respiratory gas exchange;[2] the degree of pulmonary hypertension was first closely related to the diminished systemic arterial blood oxyhemoglobin saturation and elevated carbon dioxide tension and acidosis that went with it by ourselves[3] and confirmed by others[4-8] and then this relationship was solidified by the demonstration of a pulmonary arterial pressor response to an acute hypoxic stimulus.[9-11] Enlarging the study to include the effects of acute alterations in hydrogen ion concentration,[12,13] we have now been able to show that in COPD, by far the most common cause of cor pulmonale, pulmonary hypertension (the direct inciting event that challenges the right heart) stems from two interacting stimuli: the vasoconstrictive effect of alveolar hypoxia on the small pulmonary arteries which are in contact with alveolar gas tensions, and from a similar effect of an increased hydrogen ion concentrations of the blood perfusing these vessels. These two variables can be graphically displayed (Fig. 1) or an equation used to express the relationship.[12,13,15] Thus, without requiring a measurement by cardiac catheterization, the values for pulmonary arterial pressure can now be obtained using arterial blood gas analysis only.[15]*

Clearly, from the above brief summary, our present day knowledge of the causes of pulmonary hypertension in COPD has greatly expanded (Fig. 2 and Table I) and thus has changed

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*The equation is found on page 906 of Reference 15 and is based on the work originally published in References 12 and 13.

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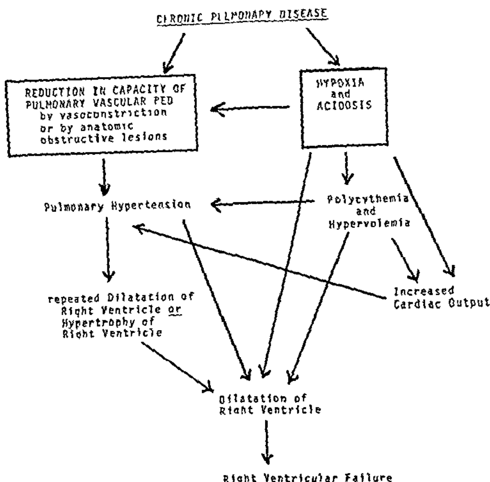


Fig 2 Chronic pulmonary disease produces cor pulmonale via two basic mechanisms—reduction in the capacity of the pulmonary vascular bed or by anatomic vascular lesions (see Table I for specific disease entities). The commonest pathway (that on the right of the diagram) starts with the altered blood gases and acidosis and moves into polycythemia and hypervolemia with increased cardiac output—these latter acting to increase the pulmonary hypertension already unleashed by the direct vasoconstricting effects of hypoxia and acidosis. Blood volume, possibly blood viscosity, increased output and direct hypoxic and acidemic effects on the myocardium invoke right ventricular dilatation and failure. This form of pulmonary hypertension and cor pulmonale is reversible with correction of the hypoxia and acidosis. If the episodes of hypoxia, acidosis and pulmonary hypertension are repetitive enough, right ventricular hypertrophy also can occur but today usually is a late manifestation of untreated cases. The second (left hand in the diagram) pathway depicts a much rarer form of cor pulmonale in which vascular occlusive lesions create the pulmonary hypertension and this situation is not reversible, and eventually progresses to right heart involvement and failure.

heart disease. Unfortunately, this does not always obtain in published studies. The mechanism of the development of cor pulmonale in COPD (see Fig 2 and Table I) appears to rest firmly on physiologic variables and since the outstanding studies of Heath, Brewer, and Hicken[30] confirmed Cromie's original work in 1961,[26] the old concept that anatomic lung destruction or pulmonary vascular lesions play a role in this right ventricular disease—a point of discussion until this work and unfortunately still published in some textbooks[31]—can now be discarded with confidence.

The normalcy of the left ventricle in cor pulmonale has been under study for some years and perhaps seems to be an area of disagreement even today. The problem arose when autopsy studies done years ago, as summarized by Weisse,[32] suggested the presence of left ventricu

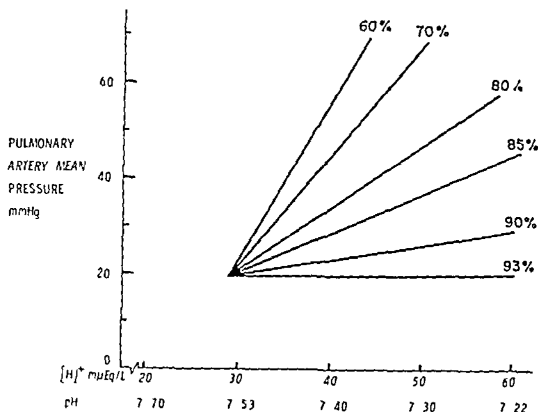


Fig 1 Graphic representation of the relationship between pulmonary artery mean pressure and blood hydrogen ion concentration considering arterial blood oxyhemoglobin saturation as a fixed parameter in 43 patients with chronic obstructive lung disease [14]

the whole face of the disease cor pulmonale as far as therapy is concerned Indeed, this cardiac disorder has moved from being universally fatal 30 years ago to being curable and even preventable in adults and in children [16,21] As seen in Fig 3 the therapeutic attack can and must occur before cardiac involvement and as soon as pulmonary hypertension appears in COPD Only in a very small percentage of instances—those in which the primary pulmonary disease is either a restrictive fibrotic or granulomatous process or repetitive pulmonary emboli with chronic pulmonary vascular occlusion—is the pulmonary hypertension intractable and prognosis poor once right heart failure appears The regimen employed by our group[17] and similar ones including those used in pediatrics [18,22] especially the recent extensive therapeutic planning described by Petty, Hudson Neff [21] and formalized so well by the InterSociety Commission for Heart Disease Resources [22] have yielded good fruit for our patients with cor pulmonale due to COPD It would seem as if all attention now should be turning first to the preventative aspects of cor pulmonale[20] (which really is prevention of pulmonary hypertension), and then to prevention of COPD itself [23,26] And yet the situation is not that salubrious

As one reviews the expressions in the recent literature regarding cor pulmonale there are some disquieting features as well as some areas of disagreement It is useful therefore, to review some of these, and then to try to envisage the future of the management of cor pulmonale

The definition of cor pulmonale (pulmonary heart disease) is now fairly universally accepted as alteration in structure or function of the right ventricle resulting from disease affecting the structure or function of the lung or its vasculature this specifically excludes the alterations resulting from disease of the left ventricle or congenital heart disease [20] Clearly we now know that neither right heart failure (a criterion used in the past[27]) nor right ventricular hypertrophy[28] (a diagnosis difficult to make clinically) are essential to its definition Cardiac enlargement due to right ventricular (RV) dilatation alone [29] in the presence of this form of pulmonary hypertension suffices This RV dilatation often disappears after successful therapy of cor pulmonale and lowering of the pulmonary hypertension Indeed with modern management of COPD this RV dilatation may be the earliest and only cardiac sign of cor pulmonale Hence statistics as to prognosis and incidence of cor pulmonale in any population will only be valid using this definition of pulmonary

Table I Diseases causing cor pulmonale[17 19]

Adults

I Diseases associated with hypoxia, acidosis and pulmonary vasoconstriction
1 Chronic obstructive pulmonary diseases conditions producing chronic severe airway obstruction such as chronic bronchitis pulmonary emphysema, and bronchiolitis.
2 Neuromuscular diseases affecting either the respiratory center or the respiratory muscles (chest and diaphragm)
3 Deformities of chest cage kyphoscoliosis and surgical or traumatic alterations of chest cage or diaphragm
4 Obesity (in some patients)

II Diseases causing anatomic obstructive lesions of pulmonary vascular bed
1 Multiple pulmonary emboli
2 Restrictive pulmonary fibrosis with fibrosing or granulomatous processes and, rarely the massive fibrosis of healed tuberculosis and radiation fibrosis.
3 Pulmonary arteritides
4 Sickle cell disease with pulmonary emboli and thrombosis.
5 Schistosomiasis
6 Metastatic lesions.

Children

I Diseases associated with hypoxia acidosis and pulmonary vasoconstriction
1 Obstructive airway disease such as fibrocystic disease (the most common cause of cor pulmonale in children) severe bronchitis bronchiolitis severe asthma upper airway obstruction due to hypertrophied tonsils adenoids or tongue pulmonary lymphangiectasis.
2 Neuromuscular diseases (as in adults) affecting the respiratory center or respiratory musculature
3 Deformities of chest cage kyphoscoliosis congenital chest distortions involving ribs and diaphragm
4 Obesity (a rare cause)

II Diseases causing anatomic obstructive lesions of pulmonary vascular bed
1 Diffuse interstitial fibrosis, causing restrictive lung disease seen in chronic pneumonia, sarcoidosis hemosiderosis Hamman Rich syndrome Mikity Wilson disease
2 Multiple pulmonary emboli (uncommon) seen in sickle cell anemia, rheumatic fever bacterial endocarditis schistosomiasis, in ventriculovenous shunts for treatment of hydrocephalus, pulmonary thrombosis in nephrotic syndrome severe dehydration or sepsis
3 "Primary pulmonary hypertension.

acidosis represent the initial stages leading to cor pulmonale (Fig 2) and so with the now commonplace use of arterial blood gas analysis (ABG) in most hospitals we have at hand the means of controlling and even preventing cor pulmonale in COPD This concept and philosophy of the reversibility of the circulatory derangements is essential to the successful treatment of this most common form of cor pulmonale[21] The earlier one suspects and documents cardiac involvement the easier it is to treat and one regrets such statements in the literature as in clinical practice it is not very important to establish whether a patient with COPD has early chronic cor pulmonale [53] Without this conviction of the reversibility of cardiac complications the herculean task of managing these often difficult, as well as seriously ill patients will not be shouldered by their physicians and nursing adjuvants.

By contrast, the course of cor pulmonale in restrictive pulmonary disease and anatomic obstructive lesions of the pulmonary vascular bed is much less amenable to therapy or change and actually the cardiac involvement often marks the terminal phase in such diseases as the diffuse pulmonary fibroses However even here with therapy the life expectancy can be as long as seven to eight years after cor pulmonale is diagnosed.[46] In cor pulmonale due to multiple pulmonary emboli there also is reason to think that improvement is occurring This is discussed in an outstanding review by McIntyre Sasahara and Sharma[54] who point out that the therapy of each individual attack of pulmonary embolism has improved and that the investigations of fibrinolytic agents acting to dissolve clots hold promise It is logical to extrapolate therefore that multiple occlusive episodes may decrease in number and in the degree of occlusion—both factors that would make long term pulmonary hypertension and eventual cor pulmonale less likely

Thus in the present era of more effective therapies and prevention of cor pulmonale prognosis of cardiac complications is better than in the past but we are still faced with a somewhat

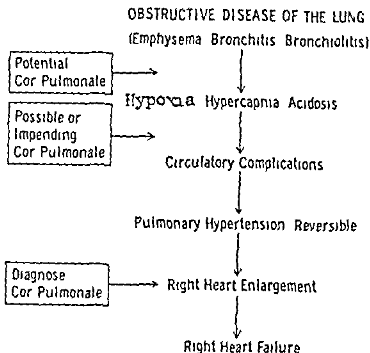


Fig 3 Schema of the serial steps in the development of cor pulmonale in obstructive diseases of the lung [14]

lar hypertrophy in a few cases of cor pulmonale These studies however, are open to review and will probably not be acceptable, since necropsy studies in recent times fail for the most part to confirm them Heath, Brewer, and Hicken[30] have discussed the critical details of determining left ventricular mass in necropsy specimens by new methods and recent measurements of myocardial fiber diameters[33] as well as details of myocardial mitochondrial numbers and surface areas [34] indicate sparing of the left ventricle in cor pulmonale Obviously, more such studies are needed Functionally recent studies[35 36] have also indicated no left ventricular dysfunction in cor pulmonale and indeed if there were any found it was the result of a separate left ventricular disease [37 38] The best summary of our present knowledge of the normalcy of the left ventricle in cor pulmonale is by Davies and Overy,[35] and they point out that the theoretical suggestions concerning deleterious effects of abnormal blood gases, especially hypoxia, on myocardial metabolism[39 40] are incorrect and that new methods confirm a normal left heart

The presence of arrhythmias in cor pulmonale deserves review As stated in 1960 [17] chronic arrhythmias i e those resulting in the permanent loss of sinus rhythm, are not a part of the over all picture of pulmonary heart disease, as they are for instance, in rheumatic or arteriosclerotic disease Recent general surveys of cor pulmonale confirm this statement In Padmavati and Raizada's[41] series of 544 patients with cor pulmonale, they do not mention any arrhythmias and Zarraby and Ghafour's[42] 100 patients had a low incidence of arrhythmias (4 per cent) This does not imply, however, that arrhythmias are not seen in patients with cor pulmonale Rather, they often appear during acute hypoxic episodes and disappear with improvement [1 43] They can be of all types and serve as a warning signal of acute respiratory failure and as Hudson and coworkers[43] stress if they are seen a check must be made on blood gas abnormalities, drug excess (digitalis and bronchodilators[17] especially) and hypokalemia It is suggested[44] that acute hypoxia produces mesencephalic stimulation with enhancement of autonomic discharge, especially via the sympathetic division and this provokes cardiac arrhythmias Thus acute respiratory insufficiency can be and often is accompanied by arrhythmias and these can be the first clinical evidence of sudden severe deterioration in gas exchange The situation is likely to be critical on all fronts and therapy must be broad based, i e both respiratory and anti arrhythmic

The prognosis of cor pulmonale is a subject on which much has been written It is crucial, however, to recognize the difference between the prognosis of the underlying lung disease and the prognosis of the cardiac complication of the lung disease For example, in COPD the long term prognosis of the lung disease is not very good as yet, and with the onset of respiratory insufficiency (as defined by severe abnormalities of gas exchange) the outlook can become ominous [45] In the same disease, however, right heart failure and enlargement have been repeatedly shown to be reversible and even patients with repeated episodes of right ventricular failure remain alive for long periods—five to 17 years in our own series[46] as well as 14 years in Padmavati and Raizada s[41] series in India and 10 to 12 years in Sadoul s[47] series in France Indeed, Heath[34] has shown that right ventricular hypertrophy itself can be reversible If therapy is intensive and modernized,[17 21 48 50] the comparison of mortality rates for patients with cor pulmonale resulting from COPD has improved[47 50 51] as compared to the mortality figures acquired in the days before intensive therapy was the rule [52] Also the effective treatment of a known adverse complication of COPD (cor pulmonale) lowers the mortality of the basic obstructive lung disease [51] Hypoxia and

in its most common form i e in COPD One must agree with Petty[64] that today we have effective means of caring for the majority of respiratory cripples Therapy for lung disease now appears even to have reduced the expected rate of pulmo nary function deterioration in some patients Surely with improved gas exchange and early detection of respiratory insufficiency the outlook for patients with respiratory diseases leading to cor pulmonale is better today than it was 30 years ago[65]

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discouraging outlook as far as some of the basic lung diseases themselves, especially COPD, are concerned.

In considering present day therapy in cor pulmonale there is no controversy about the need to attack the pulmonary insufficiency in COPD (as defined by a PO_2 of less than 50 mm Hg and a PO_2 of more than 50 mm Hg), and since it has been shown that circulatory disturbances are the rule below arterial oxyhemoglobin saturation levels of 85 per cent[14,55] (Fig 1) the emphasis is upon control of the arterial blood gases (ABG) Indeed it is probably true that the two greatest advances in the modern handling of patients with cor pulmonale due to COPD are (1) the ready and now commonplace use of arterial blood gas analysis in most hospitals today allowing for appraisal of respiratory insufficiency much as diabetic control is followed by metabolic measurements and (2) the successful use of artificial respiratory ventilatory aids both in and out of the hospital by these patients The repeated monitoring of ABG is a basic and absolute *necessity in following patients with COPD* There should be at least a monthly test until it is proved that stability is achieved During attacks of acute respiratory insufficiency the therapeutic effects can only be gauged by ABG values It is likely that, in the modern era of cor pulmonale the onset of the cardiac complications of COPD is best diagnosed from hypoxia and acidosis in the ABG change in heart size by x ray and the appearance in the electrocardiogram of transitory negative T waves in Leads V_1 V_3 (right V leads)[15] *since edema of the legs is seldom seen in this age* of powerful diuretics and since the liver size is *deceptive in* COPD patients with a low diaphragm

The use of oxygen in treating patients with COPD and cor pulmonale has been carefully considered throughout the recent past It is clear that high flow O_2 therapy *without* the assistance of a mechanical ventilatory aid such as is provided by *intermittent* positive pressure breathing (IPPB) devices, or the self regulatory volume respirators or tank or suit respirators, can induce carbon dioxide narcosis and coma With mechanical ventilatory aids[56,57] normalization of ABG is achieved and if the aid can be used at home in a regular fashion i e, for 30 minutes three to five times a day, control of hypoxia and its consequences is fairly good A new and recent therapy the use of continuous nasal *low flow* oxygen (1 to 3 L per minute) without mechanical ventilation has brought new improvements in heart and lung function in COPD[2,58-60] This therapy is best used as near to 24 hours a day as possible and is indicated when IPPB at home is difficult It should be maintained at least 15 to 18 hours per day[59] Careful checking with serial arterial blood determinations has shown that respiratory depression due to increase in carbon dioxide tension appears to be unusual, but must be watched for[59] The goal of such therapy is to keep the arterial oxygen tension between 55 and 60 mm Hg at rest

The use of digitalis in cor pulmonale is no longer controversial and is clearly recommended by several groups[2,17,19,27,61] Certain practical problems remain however Both digitalis and diuretics are important agents in the management and rehabilitation of patients with cor pulmonale in heart failure and yet it must be stressed that arrhythmias will easily appear with over use of digitalis bodies in these hypoxic patients and hypokalemia after diuresis can also bring ectopic activity Thus, only careful and balanced appraisal of dosage of these two agents will result in proper handling of digitalis in cor pulmonale

The value of respiratory stimulants remains a topic of debate[62] and has not been accepted as part of most respiratory care programs The resultant increased work of breathing on already fatigued respiratory muscles is a limiting feature in this concept. The problem of fatigued musculature has only recently been studied quantitatively[63] and yet the understanding of the importance of diaphragmatic weakness has led to its treatment by resting the diaphragm and other inspiratory muscles with a tank respiratory for extended periods of time By thus supplying the breathing energy on a long term basis with the use of tank respirators at home the muscles can recover and permit *only intermittent* use of assisted breathing later on Sleeping in tank or suit respirators can be of great value in these instances

Summary

In reviewing the present day status of cor pulmonale it is clear that considerable progress has been made in almost all instances of the disease It is clearly a preventable form of heart disease in most cases and it is treatable and curable

Electrophysiology and pharmacology of cardiac arrhythmias VI Cardiac effects of verapamil

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Verapamil a papaverine derivative was introduced as a coronary vasodilator in 1962 by Haas and Hartfelder [1] Although it was their impression that the drug was a beta adrenergic blocking agent studies by other investigators failed to confirm this supposition [2,3] Additional studies in experimental animals demonstrated that the drug was a potent antiarrhythmic agent [4-6] In an investigation of the comparative effects of verapamil quinidine pronethalol and MJ 1999 (sotalol) on a variety of experimentally induced canine cardiac arrhythmias the most consistently effective drug was quinidine (89 per cent of all arrhythmias) [5] Verapamil was as effective as quinidine with respect to hydrocarbon epinephrine and ouabain induced arrhythmias was somewhat less effective (70 per cent) against arrhythmias due to coronary ligation and modified only 40 per cent of aconitine induced atrial arrhythmias [5] Other studies on dogs cats and guinea pigs [4,6,7] have shown comparable efficacy for verapamil with respect to ventricular fibrillation induced by ouabain coronary ligation and chloroform-epinephrine

Verapamil has been used successfully as a clinical anti arrhythmic drug since 1966 [8] but is not approved for use in the United States Recently there has been a heightened investigative interest in the drug because it has been demonstrated to block the weak inward current which flows through the slow channels in cardiac fibers and which may be carried by Ca^{++} [9,10] It has been proposed that this slow current may be significant in the genesis of certain cardiac arrhythmias [11-13]

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Clinical use

Published studies of the antiarrhythmic effects of verapamil are limited, and refer almost exclusively to intravenous administration The largest single series of cases has been reported by Schamroth and colleagues [14] In 115 cases of atrial fibrillation the ventricular response was slowed in 111 Of 15 instances of atrial flutter ventricular response was slowed in 11 and sinus rhythm restored in four All of 20 cases of paroxymal supraventricular tachycardia and three of junctional tachycardia returned to sinus rhythm The response of ventricular arrhythmias was less dramatic only 11 of 23 instances of ventricular premature depolarizations responding to verapamil A number of other smaller series have shown similar results In these studies supraventricular tachycardias [15-18] and atrial fibrillation [16,19] showed uniformly good responses to verapamil approximating those in the Schamroth series [14] In one of these series six of 12 instances of atrial flutter returned to sinus rhythm. [17] Also of note is a rather high degree of efficacy (greater than 90 per cent) in two series of cases of tachycardias associated with preexcitation

Clinical pharmacology

Little has been reported concerning the clinical pharmacology of verapamil For the therapy of arrhythmias most published investigations re

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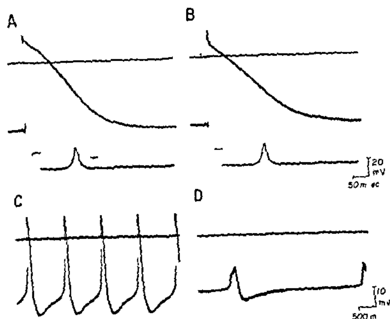


Fig 2 Effects of verapamil on specialized conducting fibers from normal and diseased human atria *Panels A* and *B* are from a segment of normal human atrium stimulated at a cycle length of 800 msec *A* is a control In *B* after 30 minutes of superfusion with verapamil 1 mg/liter resting membrane potential, action potential amplitude and V_{max} are unchanged However the voltage at which the plateau originates is decreased and the slope of phase 2 is increased. *Panels C* and *D* are recorded from an isolated sample of diseased human atrium *C* is a control record of the spontaneous rhythm occurring in this tissue In *D* following 7 minutes of superfusion with verapamil 1 mg/liter the maximum diastolic potential the slope of phase 4 and the spontaneous rate have decreased, and action potential amplitude is markedly diminished. Within 1 minute the preparation became quiescent For both preparations $[K^+]_o$ = 4 mM $[Ca^+]_o$ = 2 7 mM Temp = 37 C Both samples were obtained from human right atria as part of the routine cannulation procedure for cardiac bypass (Hordof A and Rosen, M)

somes and has no effect on CA activated ATPase and therefore apparently does not exert its effects at the e sites[25,26] Recent investigations have suggested that although verapamil does block the inward current carried by Ca it also inhibits a slow current carried by Na [27] Hence, its primary action may be on the slow channel itself (and any ions moving through it) and not specifically on calcium

Effects of verapamil on electrophysiologic properties of normal cardiac fibers

The blocking effect of verapamil on the slow inward current may be largely responsible for its antiarrhythmic effects and represents a different mechanism of action from that exhibited by most other antiarrhythmic agents [7] Procainamide quinidine lidocaine and some beta receptor blocking agents have local anesthetic effects and during phase O depolarization interfere with sodium entry in cells with fast response action potentials[28] As a result they decrease phase O upstroke velocity (Vmax) and action potential amplitude A reduction in these parameters causes depression of conduction and this may be a major factor underlying the efficacy of these drugs in the therapy of atrial and ventricular arrhythmias Verapamil has little or no effect on action potential amplitude or Vmax in cells with fast response action potentials in the ventricular specialized conducting system (Fig 1) and the atria (Fig 2 *A* and *B*) As an explanation for this phenomenon it has been noted that low or therapeutic concentrations of verapamil decrease the rapid inward Na current by only 6 per cent.[10]

Antiarrhythmic drugs may modify arrhythmias by altering the recovery of excitability and the refractory period of cardiac cells Shifts in the membrane responsiveness curve induced by these agents may affect conduction of premature impulses and thereby abolish arrhythmias by

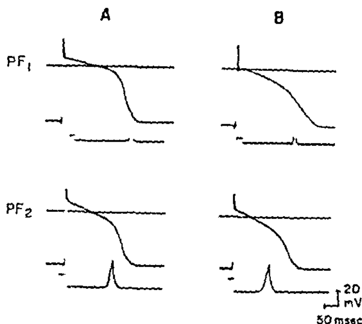


Fig 1 Effects of verapamil on normal canine cardiac Purkinje fibers For these and subsequent records the upper trace is the action potential and the lower shows a 200 V/sec calibration followed by the electronic differentiation of the maximum rate of rise of phase O (V_{max}) *Panel A* is a control record of two Purkinje fiber action potentials PF 1 and PF 2 *Panel B* shows the same action potentials 30 minutes after onset of superfusion with verapamil 1 mg/liter Note that this concentration of verapamil has no effect on action potential amplitude or V_{max} or on resting membrane potential However the voltage at which the plateau originates is decreased and the slope of phase 2 repolarization is increased by verapamil These changes are consistent with the block of a slow inward current such as that carried by calcium ion *Cycle length 800 msec* $[K^+]_o = 4$ *mM* $[Ca^{++}]_o = 2.7$ *mM* Temp = 37 C (Rosen M and Merker C)

port the slow intravenous administration of 10 mg (range 5 to 15 mg) Information concerning its metabolism and excretion is incomplete and has been collected largely in studies of experimental animals in which verapamil-^{14}C was administered[20]

Following oral administration of verapamil 5 mg per kilogram of body weight the drug is 80 per cent absorbed within three hours [1] Maximal plasma levels are attained in two hours after oral or intramuscular administration and radioactivity is no longer measureable in the plasma 48 hours after a single dose On intravenous administration, distribution to the various body compartments is rapid only 1 per cent of the dose being detectable in plasma 15 minutes following injection[21]

Metabolism of verapamil occurs largely in the liver, as N and/or O demethylation[20,21] The metabolic products reportedly have little biologic activity Eighty per cent of a given dose is excreted as metabolites in the bile within 10 hours of drug administration Another 20 to 25 per cent, as metabolites is excreted in urine over 48 hours The plasma t½ for the major metabolites is 10 hours

The drug has been reported to induce hypotension, bradycardia and asystole,[18] although the clinical incidence of these phenomena has not been estimated accurately There are also reports of induction of high degrees of heart block in patients with clinical evidence of disease of the atrioventricular conducting system[22] A major contraindication to verapamil administration is reported to be recent or concomitant administration of β adrenergic blocking agents Asystole occurring rapidly after verapamil administration in this instance has been documented[18,23] Intravenous administration of β adrenergic amines has been recommended for therapy of verapamil overdose[20]

Mechanisms of action

The observation that verapamil markedly depresses contractility of ventricular muscle fibers without altering the transmembrane action potential suggested to Fleckenstein[24] that the drug interfered with Ca^{++} mobilization or utilization Subsequent investigators have attempted to localize and further define the actions of verapamil In voltage clamp experiments on cat ventricular trabeculae verapamil caused a complete disappearance of the late slow inward current which may be carried by Ca^{+}, with only minor suppression of the initial rapid inward Na^{+} current which is responsible for the fast upstroke of the cardiac action potential[10] The threshold potential for initiation of the slow inward current was not markedly altered despite the reduction in its magnitude The depressant effect of verapamil on the slow inward current in these voltage clamp experiments was overcome by increasing the Ca^{++} concentration gradient across the cell membrane It was therefore concluded that a major action of verapamil is to block the slow inward Ca^{++} current in cardiac fibers[10]

Verapamil decreases $45Ca^{++}$ uptake by ventricular trabeculae It has been suggested that the drug reduces the amount of Ca^{++} stored at membrane located binding sites and therefore the amount of Ca^{++} available for release from these sites[5] Verapamil does not modify Ca^{++} uptake binding or exchange by cardiac micro

Cardiac fibers in the sinus and atrioventricular nodes and the mitral valve leaflets which have slow response action potentials under normal conditions may also be involved in the genesis of atrial arrhythmias Spontaneous impulse initiation occurs in cardiac fibers in the mitral valve leaflets when exposed to catecholamines[32] In addition in studies of monkey hearts fibers on the mitral leaflets have been shown to exhibit delayed afterdepolarizations which may result from the slow inward current (Fig 3) The amplitude of the afterdepolarization increases when catecholamines are superfused, and they may reach threshold potential When this occurs automatic impulse initiation commences Verapamil in concentrations which have no effect on normal atrial action potentials abolishes the delayed afterdepolarizations produced by catecholamines and thereby prevents spontaneous activity in these mitral valve fibers[33]

Similar delayed afterdepolarizations occur in atrial specialized fibers when exposed to toxic concentrations of digitalis[34] Automatic impulse initiation occurs in these fibers when the afterdepolarizations reach threshold and may be responsible for some digitalis induced atrial arrhythmias Verapamil abolishes the afterdepolarizations induced by digitalis in human atria and may suppress arrhythmias in this way (Hordof A and Rosen M preliminary observations)

Supraventricular tachycardias may result from continuous reentry of impulses utilizing either the sinus or atrioventricular node as part of the reentrant pathway[12,13] Reentry may be initiated by a premature impulse which conducts through the node very slowly and then returns to the atria after they recover excitability Verapamil exerts potent depressant effects on sinus and atrioventricular nodal function and in low concentrations it prolongs the effective refractory period of the atrioventricular node[35] A study on the isolated, superfused rabbit right atrium has suggested a mechanism by which verapamil may abolish certain supraventricular tachycardias[36] Whereas premature impulses conduct slowly through the node and reenter the atrium prior to exposure to verapamil after verapamil conduction of these premature impulses is blocked in the node and reentry *is* prevented (Fig 4) This effect of verapamil occurs in concentrations (approximately 0 1 mg / liter) which do not significantly modify conduction of the normal atrial impulse and may be due to a prolongation in the time dependence for recovery of excitability of AV nodal cells A similar effect may occur in the sinus node although it has not been demonstrated.

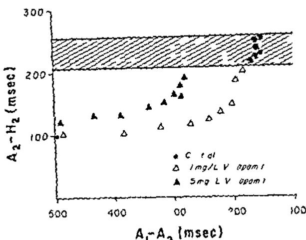


Fig 4 Effect of verapamil on conduction of premature atrial impulses in the AV node of the isolated rabbit heart and on the initiation of AV nodal tachycardia The heart is being driven at a cycle length of *600 msec* and a premature atrial impulse induced after every 7th to 10th basic impulse *Abscissa* Coupling interval between the last basic atrial impulse (A_1) and the premature atrial test pulse (A_2) *Ordinate* Conduction time of the premature impuls through the AV node (A_2 H_2) Prior to drug superfusion (*solid circles*) conduction time of the premature impulse in the AV node increased as the A_1 A_2 interval was shortened until a critical degree of conduction delay occurred whereupon rapid sustained atrial tachycardia was initiated This critical degree of AV nodal conduction delay needed to initiate tachycardia is indicated by the shaded area and all solid circles within the shaded area induced tachycardia The arrhythmia resulted from reentry utilizing the AV node as part of the reentrant pathway Further shortening of the A_1 A_2 interval resulted in conduction block of A_2 in the AV node at a coupling interval of 140 msec (control effective refractory period) After superfusion with 0 1 mg /liter verapamil for 15 minutes (*open triangles*) conduction of premature atrial impulses was not greatly affected until the effective refractory period of the node was reached. The effective refractory period occurred at a longer coupling cycle length between A_1 and A_2 than it did in the control (A_1 A_2 = 180 msec) and as a result the conduction delay needed to initiate tachycardia never occurred (no open triangles occur within the shaded area) 0 5 mg /liter verapamil (*solid triangles*) slowed conduction of premature impulses and markedly lengthened the effective refractory period to 290 msec As a result the conduction delay needed to initiate tachycardia did not occur (no solid triangles in shaded area)

Verapamil depresses the amplitude of action potentials in the upper and mid atrioventricular node without altering resting potential (Fig 5) This effect is more pronounced at rapid atrial

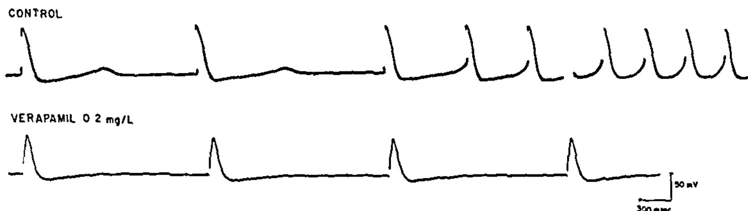


Fig 3 Effect of verapamil on a catecholamine induced delayed afterdepolarization of a monkey mitral valve fiber and triggered sustained rhythmic activity In the top panel the fiber is being stimulated at a cycle length of 630 msec Note the delayed afterdepolarization after the first two driven action potentials. After the third driven action potential the amplitude of the afterdepolarization reaches threshold potential and sustained rhythmic activity begins and accelerates (discontinuous trace) In the bottom panel after superfusion with 0 2 mg /liter of verapamil the delayed afterdepolarization has been abolished and the upstroke velocity and amplitude of the mitral valve action potential diminished. Now sustained rhythmic activity cannot be initiated at a stimulus cycle length of 630 msec

mechanisms we have described previously [12,13] Verapamil accelerates early repolarization in rabbit atrial fibers[7] and in fibers from normal human atrium (Fig 2*A* and *B*) but does not significantly alter the time for complete repolarization and has not been reported to affect the relative and effective refractory periods

In normal Purkinje fibers, low concentrations of verapamil (approximately 1 mg / liter) shift the plateau phase of repolarization to more negative potential levels but do not significantly alter the time for complete repolarization [29,30] Further the effective refractory period of normal Purkinje fibers is not significantly changed [29] Verapamil does not shift the membrane responsiveness curve of normal Purkinje fibers except at very high concentrations[29] and presumably would not significantly alter conduction of premature impulses Only in high concentrations (5 to 10 mg / liter) does verapamil prolong the repolarization time and effective refractory period of normal Purkinje fibers and depress membrane responsiveness [29] Therefore it is unlikely that verapamil exerts its antiarrhythmic effects by virtue of its actions on refractoriness and responsiveness of normal cells

Verapamil does depress spontaneous diastolic depolarization which originates at normal levels of membrane potential in canine Purkinje fibers [29] This may represent an antiarrhythmic action of the drug The mechanism of this inhibitory effect on normal spontaneous diastolic depolarization has not been identified

Effects of verapamil on electrophysiologic events responsible for arrhythmias

The most pronounced electrophysiologic effects of verapamil are exerted on cardiac fibers with slow response action potentials These action potentials may induce both atrial and ventricular arrhythmias by a variety of mechanisms which we have described previously [11,13]

A Atrial and atrioventricular junctional arrhythmias There may be several bases for the high degree of efficacy of verapamil against atrial arrhythmias Microelectrode studies of isolated superfused cardiac tissue obtained at surgery from diseased human atria have demonstrated action potentials arising from low levels of membrane potential with slow upstroke velocities and reduced amplitudes [31] These may be slow responses (Fig 2 *C* and *D*) Spontaneous diastolic depolarization and automatic activity are often present in such fibers Whereas verapamil does not significantly alter the normal atrial action potential (Fig 2 *A* and *B*), it markedly depresses amplitude velocity of depolarization and conduction in the depressed atrial fibers and completely abolishes automaticity (Fig 2, *C* and *D*) These effects are probably due to inhibition of the slow inward current by verapamil The depression of action potential amplitude phase O depolarization and conduction may abolish reentry in these diseased atria while the depression of abnormal automaticity is probably also a significant antiarrhythmic action

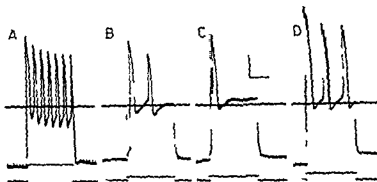


Fig 6 Effect of verapamil on Ca^{++} dependent slow response in canine Purkinje fibers The preparation is being superfused with a Na^{+} free solution in which Na^{+} has been replaced by TEA Ca^{++} in the perfusate is 16 8 mm In each panel a 10 sec pulse is passed through an intracellular microelectrode during the time indicated by the solid horizontal line in the lower trace depolarizing the fiber to −50 mV and resulting in slow response action potentials *Panel A* is the control In *panel B* after superfusion with 1 mg /liter of verapamil the frequency of slow response activity has decreased and there is a diminution in the amplitudes of the action potentials In *panel C* after superfusion with verapamil 2 mg /liter there is a further decline in both frequency of activity and action potential amplitude In *panel D* the $[Ca^{++}]_o$ was increased to 32 mM Note the increase in action potential amplitude and the restoration of spontaneous activity Vertical calibration = 15 mV Horizontal calibration = 5 sec (From Cranefield P F Aronson R S and Wit A L Effect of verapamil on the normal action potential and on a calcium dependent slow response of canine cardiac Purkinje fibers Circ Res 34 204 1974 Reproduced by permission of The American Heart Association Inc)

and 0 5 to 0 75 mg per kilogram of body weight induce atrioventricular block [17] Intraarterial administration of the drug into the coronary circulation results in decreased P wave voltage and the occurrence of junctional rhythms and A V block [43] The effects of verapamil on heart rate cannot be abolished by atropine [7] suggesting that the action of verapamil on sinus rate and AV conduction is not mediated by the vagus

That verapamil s action as a cardioactive drug is not mediated by β adrenergic receptor blockade is suggested by studies of the effects of stellate ganglion stimulation on myocardial function [25] In addition left ventricular contraction and work and O_2 consumption (A V O_2 difference) were not modified by verapamil 0 5 mg per kilogram of body weight but were altered by the same dose of propranolol.[25]

In clinical studies of the effects of verapamil His bundle recording techniques and atrial stimulation have been used to determine its effects on impulse propagation in the human heart That verapamil does in fact act rather selectively to depress conduction in the atrioventricular node is attested to by the observation that it prolongs the A H interval in patients in sinus rhythm [44,45] As for sinus node function it depressed sinus node recovery time following overdrive suppression by 10 to 15 per cent.[45]

Summary

It is clear from clinical and experimental data that have been reported thus far that verapamil is highly effective in the therapy of cardiac arrhythmias and that it acts by a different mechanism than most of the commonly used antiarrhythmic drugs The available clinical data indicate that on intravenous administration verapamil is as good as and perhaps superior to quinidine procainamide and propranolol for the therapy of many atrial arrhythmias Unfortunately the extent to which it is useful as long term prophylaxis has not yet been reported, nor has its toxicity during protracted oral administration

The effects of verapamil on cardiac action potentials clearly indicate that it modifies the slow response to a much greater extent than the fast response Studies of cardiac tissues from diseased human atria have indicated that slow response action potentials occur frequently [31] It is possible that such action potentials are responsible for the reentrant and automatic arrhythmias which occur in association with clinical cardiac disease Whether the efficacy of verapamil in the therapy of atrial arrhythmias is primarily due to abolishing slow response activity in diseased atrial tissues or to suppression of propagation through the atrioventricular node is uncertain However

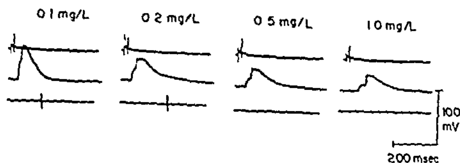


Fig 5 Effect of verapamil on an action potential recorded from a fiber in the upper region of the AV node The top trace in each section is an atrial electrogram and O potential The middle trace is an action potential of an upper nodal cell and the bottom trace is a His bundle electrogram Action potentials were recorded from the nodal fiber after superfusion of the preparation for 20 minutes with 0 1 mg /liter of verapamil Impalement was then maintained as the drug concentration was increased to 0 2 mg /liter 0 5 mg /liter and 1 0 mg /liter Note the decrease in amplitude of depolarization with increasing drug concentration without any loss of maximum diastolic potential At 0 2 to 1 0 mg /liter of verapamil the peak of the action potential fell well short of reversal After 0 5 mg /liter of verapamil there was AV block between the recording site and the His bundle After 1 mg / liter there was some conduction delay between the atrial site and the AV node (From Wit A I and Cranefield P F The effects of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanism by which it arrests in reentrant AV nodal tachycardia Circ Res. 35 413 1974 Reproduced by permission of The American Heart Association Inc)

rates Such an electrophysiologic effect is probably the cause for the depression and block of conduction through the atrioventricular node (particularly at rapid atrial rates) which occurs after verapamil [37] If the atrioventricular node is part of a reentrant pathway responsible for a supraventricular tachycardia the inability to conduct impulses at a high frequency may terminate or prevent reentry and the tachycardia Verapamil induced depression of atrioventricular nodal action potentials and conduction is almost certainly the mechanism by which it decreases the ventricular response in atrial flutter or fibrillation

Verapamil decreases the action potential amplitude and spontaneous firing rate of sinus nodal cells[38] as well as depressing the atrioventricular node These effects on both nodes are concentration dependent High verapamil concentrations can almost completely abolish the sinus node action potential and cause complete atrioventricular conduction block [37] Therefore inhibition of the slow response by verapamil may also be responsible for its toxic electrophysiological effects

B Ventricular arrhythmias Slow response action potentials in Purkinje fibers may be a cause of reentry and ventricular arrhythmias [12 13] Verapamil decreases action potential amplitude and the abnormal automaticity of Purkinje fibers in which the fast inward sodium current has been abolished by superfusion with a Na^+ free medium (Fig 6) [30] As yet the effects of verapamil have not been studied on slow responses occurring in the presence of high $[K^+]o$ and catecholamines or on Purkinje fibers with low resting potentials and slow rates of depolarization in diseased areas of the conducting system If verapamil does markedly diminish action potential amplitude and conduction in these fibers it would be expected to abolish reentry The ineffectiveness of verapamil against certain ventricular arrhythmias may indicate that the slow response is not always involved in arrhythmia genesis

In studies of Purkinje fibers superfused with acetylstrophanthidin or ouabain it has been noted that delayed afterdepolarizations occur in association with digitalis toxicity [39 41] As previously described these afterdepolarizations may be the basis for certain digitalis induced arrhythmias that occur clinically [42] Verapamil in low concentrations (approximately 1 mg /liter) has been shown to decrease the magnitude of the afterdepolarizations [29] an effect which may explain its efficacy in the treatment of digitalis induced arrhythmias

Effects of verapamil on the in situ heart

In studies of verapamil effects on the canine heart doses of 25 mg per kilogram of body weight have been shown to decrease sinus rate

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it is likely that the therapeutic action of the drug may result from altered propagation of an arrhythmia through the atrioventricular junction as well as from the effects of the drug on diseased atrial and ventricular tissues

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In summary to explain the puzzling observation that certain populations with a high dietary carbohydrate intake have a high tendency to diabetes and coronary artery disease and others a low tendency the postulate is made that the amount of exercise could alter the metabolic response of the body to increased dietary carbohydrate and reduce the circulating blood sugar for a given concentration of insulin. Thus exercised individuals would tend to be less diabetic and by inference less prone to the development of ischemic heart disease According to this hypothesis if a patient at risk of developing ischemic heart disease is given advice to reduce dietary lipid intake he could be advised to increase intake of carbohydrate including sucrose provided he were also advised to take more exercise

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Treatment of oat cell carcinoma of the lung

The results of treatment for cancer of the lung as a whole have tended to improve steadily over recent years, mainly because of earlier diagnosis, elimination of sepsis by antibiotics, improved anaesthetic techniques, and postoperative care

All these important factors however have failed to produce any improvement in the results of treatment for oat-cell carcinoma and some thoracic surgeons and physicians find the results of surgery so depressing that they refer all their cases for primary radiotherapy or chemotherapy Considerable interest has been shown recently in the clinical presentation of oat cell carcinoma with its ability for hormone production and also in new methods of treatment, as of the various histological varieties of bronchial carcinoma the oat cell variety has always had the worst prognosis

Most thoracic surgical units will quote cases of oat-cell car

Annotations

Dietary sucrose in relation to the development of ischemic heart disease*

Yudkin and Roddy[1] have claimed that sucrose might be instrumental in the genesis of ischemic heart disease by promoting the development of coronary artery atheroma On the other hand a very considerable body of opinion holds that the incidence of ischemic heart disease can be correlated with abnormalities in circulating lipids more particularly in the concentrations of cholesterol[2] and triglyceride[3] Alterations in the dietary sucrose intake have not thus far been shown to exert a consistent influence on circulating cholesterol and/or triglyceride concentrations and opponents of Yudkin s view ask how sucrose could promote ischemic heart disease This annotation assesses one possible relation between sucrose and ischemic heart disease It is argued that although a continued high sucrose intake may promote the development of the diabetic state and arterial disease in predisposed individuals that increased exercise could counteract this potential diabetogenic effect

The relation between dietary carbohydrate intake and triglyceridemia has been reviewed by Hulley and colleagues[4] a low carbohydrate diet is useful in the therapy of triglyceridemia whereas an extremely high carbohydrate diet increases serum triglyceride concentration There is no simple relation between carbohydrate intake and triglyceridemia because carbohydrate induced triglyceridemia can be prevented by nocturnal carbohydrate feeding[5] However in genetically predisposed subjects an increased carbohydrate diet may eventually result in an increased concentration of circulating triglycerides which may in turn have harmful effects for the development of coronary artery disease

A short term increase of dietary carbohydrate has long been thought to promote insulin sensitivity of the tissue of the body hence the practice established by Himsworth[6] of giving patients a high carbohydrate diet before a glucose tolerance test In obese subjects increased dietary carbohydrate intake may lead to hyperinsulinism[7] It is not yet known whether hyperinsulinism could lead to the insulin antagonism associated with maturity onset diabetes but a genetic factor may determine the individual s capacity to maintain hyperinsulinism or to develop absolute or relative failure of output of insulin In the development of diabetes the earliest abnormality of carbohydrate metabolism is thought to be an excessive response of plasma insulin to an elevated blood glucose and thereafter overt diabetes develops with a diminished insulin response[8] Thus increased dietary carbohydrate may be a factor leading to glucose intolerance but the issue is complex because very obese people take most of their calories as carbohydrate[7] In a study encompassing 11 countries West and Kalbfleisch[9] found a positive correlation between the incidence of diabetes and adiposity but there was also some correlation with dietary carbohydrate intake Taking their data together with those of Cleave and Campbell[10] they conclude that it seems highly probable that there is a significant association between sugar consumption and the prevalence of diabetes. This line of reasoning would explain the high incidence of diabetes mellitus and ischemic heart disea e in certain populations such as Natal Indians having a high carbohydrate intake[10,11] But why are other populations which have a high carbohydrate intake—eg many African Native populations—spared from diabetes?[10,12] One explanation might be the type of carbohydrate eaten (for example sucrose vs starch) but another explanation might be the influence of exercise on carbohydrate metabolism Thus the very hard working Zulu cane cutters in Natal have a very low incidence of diabetes mellitus in spite of a very high carbohydrate intake[10]

Exercise influences the carbohydrate metabolism of the normal and the diabetic heart In isolated hearts from normal or diabetic rats increased heart work leads to increased glucose uptake and an increased insulin effect[13] There is a direct effect of increased work on glucose transport in both the rat heart[14] and in skeletal muscle[15] Increased glucose uptake by muscle may explain why patients who are diabetic require less insulin when they are no longer resting in bed but are walking around The direct effect of acute exercise or promotion of glucose transport across the cell membrane must be of major importance because circulating immunoreactive insulin is actually decreased during acute exercise[16] Physical training results in an increased insulin sensitivity and it appears an increased capacity for glucose uptake by peripheral tissue[17] Thus it becomes reasonable to conclude that exercise may decrease the requirement for circulating insulin for a given rate of glucose uptake and hence exercise would tend to prevent the development of insulin resistance following increased dietary carbohydrate intake

The above discussion is largely based on the assumption that the type of dietary carbohydrate is not relevant and that the effects of dietary sucrose are the same as those of other carbohydrates Replacement of sugar by starch in the diet results in a fall in serum triglyceride concentration but the effect could be due to weight loss[18] When starch replaces sucrose in the diet of men in a metabolic unit there are no significant changes in serum lipids[16] immunoreactive insulin, or in the insulin response to a mixed meal[19] However in rats exposed to relatively long term increased dietary sucrose (instead of starch) there is impaired glucose tolerance[20]

Cleave and Campbell[10] claim a specifically harmful role for refined sugar compared with other carbohydrates Should this be so people taking much sucrose would need even more exercise than others on a high intake of other carbohydrates However equally good advice might be simply to avoid obesity because obese Maoris in New Zealand have an appreciably higher incidence of diabetes mellitus than do the leaner European New Zealanders although both groups consume about 11 per cent of their total calories as sucrose[21]

*Supported in part by the International Sugar Research Foundation Inc

dose not exceeding 2 000 rads so that the surgeon may elect to perform a lobectomy if thought desirable without the fear of radiation pneumonitis occurring in the remaining lobe a short course of cytotoxic drugs to cover the operation to destroy any neoplastic cells disseminated at the time of surgery and the resection of the lung tumor which the radiotherapy in itself will not have been sufficient to cure

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A retrospective case-control study of diseases associated with oral contraceptive use

In 1972 the Boston Collaborative Drug Surveillance Program undertook a large scale epidemiologic survey to evaluate associations between drug use by ambulatory patients and disease states requiring hospitalization.[1] Trained nurse monitors were stationed on general medical and surgical wards in 24 community and university hospitals in the Boston area. A detailed history of all drugs including oral contraceptives, used prior to hospitalization was obtained from approximately 25 000 consecutively admitted patients aged 20 to 75 years. Drug histories demographic data and discharge diagnoses were stored on magnetic tape

Retrospective case control analysis was used in the present study A total of 5 472 females aged 20 to 44 years was monitored From this group were selected 842 controls, consisting of premenopausal women free of any known chronic disease who were hospitalized only for acute illness (trauma, respiratory infections, gastroenteritis, appendicitis) or elective surgery None of the controls had any disorder which might contraindicate or be caused by oral contraceptive use Cases also were selected stringently Only patients having "idiopathic" venous thromboembolism with no apparent predisposing cause were included (n = 43) All cases of gallbladder disease were confirmed surgically (n = 212) Cases of benign breast tumor were confirmed histologically (n = 98)

Since oral contraceptive use becomes less common with increasing age risk ratios were age standardized[2] (Table I) The association between venous thromboembolism and oral contraceptive use is highly significant Duration of use did not influence the risk. The results of other case control studies are similar[3-5] Because idiopathic venous thromboembolism is a relatively rare event the risk may not become apparent in prospective studies[6] Enhancement of coagulability induced by oral contraceptives[7] probably explains the association with venous thromboembolism as well as other thromboembolic disorders

The association of oral contraceptive use with gallbladder disease also is significant (Table I) and has not been reported previously The disease tended to develop within the first year of oral contraceptive use Although the relative risk (2 0) is smaller than for venous thromboembolism (11 0) the attack rates attributable to oral contraceptives are similar because gallbladder disease is more common in the population, Women are known to develop gallbladder disorders more frequently than men particularly during the

Table I Risk ratios and estimated attack rates

Disease	*Age-standardized risk ratio*	*Summary* χ^2 *value (d.f = 1)*	*Significance level*	*Yearly attack rate attributable to OC s per 100 000 OC users*
Venous thromboembolism	11	57	p < 0001	60
Gallbladder disease	2 0	15 0	p < 001	79
Benign breast tumor	0 47	5 4	p = 02	—

cinoma successfully treated and surviving ten years following surgery but these cases will almost certainly have been peripheral lesions with negative lymph nodes Where an oat cell carcinoma presents in the bronchus and a positive biopsy can be obtained, then surgery alone is very rarely successful

In 1955 Bromley and Szur[1] tried the effect of combining surgery with preoperative radiotherapy in the hope of improving the long term results They gave their patients an average of 4 700 rads preoperatively on the 250 kv machine Unfortunately this resulted in a 27 per cent complication rate of late bronchopleural fistula and empyema and the method was therefore abandoned In their series of 66 patients there were 11 cases of oat cell carcinoma four of whom died soon after operation and viable cancer cells were present in the remaining seven at death

As a result of improved techniques and the introduction of cobalt radiotherapy a comparative trial of surgery and primary radiotherapy for the treatment of oat cell carcinoma was carried out by the Medical Research Council and in 1966[2] they gave a two year report There were 71 patients in the surgery series and 73 in the radiotherapy series. At 24 months 4 per cent of the surgical patients were surviving and 10 per cent of the radiotherapy patients had survived. These investigators concluded that radical radiotherapy was marginally better treatment than surgery for oat cell carcinoma

In 1969 [3] a five year follow up report on this same trial showed only one patient alive from the surgical series and three from the radiotherapy series Very recently the 10 year follow up report[4] confirmed the improved results with radiotherapy the three patients still being alive but none from the surgical series being alive

In 1968 Lennox and colleagues[5] from the London Hospital reported their results in 275 cases of oat cell carcinoma They stated a two year survival rate of 10 6 per cent for the series and concluded that surgery still has an important place in the treatment of oat cell carcinoma The Medical Research Council then initiated a further trial of cytotoxic chemotherapy as an adjuvant to surgery in carcinoma of the bronchus They published a two year report in 1971 [6] In a total of 753 patients 39 were suffering from oat cell carcinoma and they were treated by surgical excision together with either busulfan cyclophosphamide or a placebo After 24 months three of the 14 patients treated with busulfan were alive none of the nine patients treated with cyclophosphamide was alive and two of the patients treated with a placebo were alive This interim report suggests that neither of the two cytotoxic drugs used as an adjuvant to surgery improved the survival rate

In a personal series of 97 cases of oat cell carcinoma operated upon between 1951 and 1966 only nine patients survived for more than two years eight of whom had lobectomies One died after 2½ years one after four years one after five years and one after 12 years from a coronary infarction Three patients who had lobectomies are alive and well one eleven years after operation and two nine years after operation The average length of life in the 88 patients who died in under two years from operation was only 6¼ months It was because of these very poor results that the thoracic surgical and radiotherapy departments of the North Middlesex Hospital decided on a trial of surgery combined with preoperative cobalt irradiation A simple opposed pair of fields was used to cover the tumor and related mediastinal lymph nodes the normal field being 15 by 10 or 15 by 12 cm Seven daily treatments of 250 rads were given to a maximum of 1 750 rads maximum toxic dose Surgery was carried out the day after treatment was completed and no reaction in the operative field was noted As a policy decision pneumonectomy was performed wherever possible Twenty nine patients in this series were operated on between 1966 and 1969 and only one developed a bronchopleural fistula after operation Twenty four patients had a pneumonectomy and seven were alive after three years a survival rate of 24 per cent for the whole series compared with 3 per cent and 7 per cent for the M R C surgery and radiotherapy series respectively However of the 24 patients who had the combined treatment we are now advocating 29 per cent were alive and well after three years and now four years after the end of the series six are still alive and well two of them having had their operations seven years ago

We considered these results to be an improvement on any previous form of treatment and therefore decided to treat a further series of patients suffering from oat cell carcinoma with 2 500 rads preoperatively Thirty one patients were treated in this manner between 1969 and 1973 but the hoped for improvement in length of life has not been obtained It may be that the increased dosage of radiotherapy has interfered with the patient s own immunity against the disease As a result of this disappointment we are now reverting to the original dosage of 1 750 rads.

Histological examination of the specimens in the first series showed that in six of the 24 specimens the tumor was anaplastic squamous carcinoma This discrepancy was noticed in the M R C [2] trial for surgery and radiotherapy but to a lesser extent three specimens out of 37 showing squamous carcinoma adenocarcinoma and a mixture of both

The reason for finding anaplastic squamous carcinoma in the specimen following radiotherapy is not yet certain It could result from the bronchial biopsy being taken from that small part of a tumor which is indeed oat cell in nature while the predominant part of the tumor is squamous in nature It is well recognized that bronchial tumors may show several different histological patterns in any one tumor However the incidence did seem higher than such an explanation might support and therefore the possibility of change from oat cell to squamous cell appearance as a result of the radiotherapy was considered

In our second series of cases where an increased dosage of radiotherapy was used the squamoid appearance in the specimens has been even more marked In nearly a third of these cases has this change been shown This high proportion of histological difference between the bronchial biopsy and specimen appearance makes it very likely that it results from the preoperative irradiation and this finding has not been previously reported

It is clear that surgery alone is not the best treatment for oat cell carcinoma and that some form of combined therapy is likely to be more effective Cell dissemination by the bloodstream to the liver or brain or suprarenals is such a common end result for a patient with this form of cancer that possibly a triple form of therapy could improve this dismal picture Preoperative cobalt irradiation could be given to a

dose not exceeding 2 000 rads so that the surgeon may elect to perform a lobectomy if thought desirable without the fear of radiation pneumonitis occurring in the remaining lobe a short course of cytotoxic drugs to cover the operation to destroy any neoplastic cells disseminated at the time of surgery and the resection of the lung tumor which the radiotherapy in itself will not have been sufficient to cure

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3 Medical Research Council Five year follow up of the operative treatment with radiotherapy of small celled or oat celled carcinoma of the bronchus Lancet 2 501 1969
4 Medical Research Council Ten year follow up of the operative treatment with radiotherapy of small celled or oat celled carcinoma of the bronchus Lancet 63 July 14 1973
5 Lennox S C Flavell G Pollock, D J Thompson V C and Wilkins J L Resection for oat cell cancer of the lung Lancet 2 925 1968
6 Medical Research Council *Two year study of cytotoxic* chemotherapy as an adjuvant to surgery in carcinoma of the bronchus Br Med J 2 421 1971

A retrospective case control study of diseases associated with oral contraceptive use

In 1972 the Boston Collaborative Drug Surveillance Program undertook a large scale epidemiologic survey to evaluate associations between drug use by ambulatory patients and disease states requiring hospitalization [1] Trained nurse monitors were stationed on general medical and surgical wards in 24 community and university hospitals in the Boston area A detailed history of all drugs including oral contraceptives, used prior to hospitalization was obtained from approximately 25 000 consecutively admitted patients aged 20 to 75 years. Drug histories, demographic data and discharge diagnoses were stored on magnetic tape

Retrospective case control analysis was used in the present study A total of 5 472 females aged 20 to 44 years was monitored From this group were selected 842 *controls* consisting of premenopausal women free of any known chronic disease who were hospitalized only for acute illness (trauma respiratory infections, gastroenteritis appendicitis) or elective surgery None of the controls had any disorder which might contraindicate or be caused by oral contraceptive use *Cases also were selected stringently Only patients* having idiopathic venous thromboembolism with no apparent predisposing cause were included (n = 43) All cases of gallbladder disease were confirmed surgically (n = 212) Cases of benign breast tumor were confirmed histologically (n = 98)

Since oral contraceptive use becomes less common with increasing *age risk ratios were age standardized[2] (Table 1)* The association between venous thromboembolism and oral contraceptive use is highly significant Duration of use did not influence the risk The results of other case control studies are similar [3 5] Because idiopathic venous thromboembolism is a relatively rare event the risk may not become apparent in prospective studies [6] Enhancement of coagulability induced by oral contraceptives[7] probably explains the association with venous thromboembolism as well as other thromboembolic disorders

The association of oral contraceptive use with gallbladder disease also is significant (Table I) and has not been reported previously The disease tended to develop within the first year of oral contraceptive use Although the relative risk (2 0) is smaller than for venous thromboembolism (11 0) the attack rates attributable to oral contraceptives are similar because gallbladder disease is more common in the population Women are known to develop gallbladder disorders more frequently than men particularly during the

Table I Risk ratios and estimated attack rates

Disease	*Age standardized risk ratio*	*Summary* χ^2 *value* (d.f = 1)	*Significance level*	*Yearly attack rate attributable to OC s per 100 000 OC users*
Venous thromboembolism	11	57	p < 0001	60
Gallbladder disease	2 0	15 0	p < 001	79
Benign breast tumor	0 47	5 4	p = 02	—

cinoma successfully treated and surviving ten years following surgery but these cases will almost certainly have been peripheral lesions with negative lymph nodes Where an oat cell carcinoma presents in the bronchus, and a positive biopsy can be obtained, then surgery alone is very rarely successful

In 1955 Bromley and Szur[1] tried the effect of combining surgery with preoperative radiotherapy in the hope of improving the long term results They gave their patients an average of 4 700 rads preoperatively on the 250 kv machine Unfortunately this resulted in a 27 per cent complication rate of late bronchopleural fistula and empyema and the method was therefore abandoned In their series of 66 patients there were 11 cases of oat cell carcinoma four of whom died soon after operation and viable cancer cells were present in the remaining seven at death

As a result of improved techniques and the introduction of cobalt radiotherapy a comparative trial of surgery and primary radiotherapy for the treatment of oat cell carcinoma was carried out by the Medical Research Council and in 1966[2] they gave a two year report There were 71 patients in the surgery series and 73 in the radiotherapy series At 24 months 4 per cent of the surgical patients were surviving and 10 per cent of the radiotherapy patients had survived. These investigators concluded that radical radiotherapy was marginally better treatment than surgery for oat cell carcinoma

In 1969 [3] a five year follow up report on this same trial showed only one patient alive from the surgical series and three from the radiotherapy series Very recently the 10 year follow up report[4] confirmed the improved results with radiotherapy the three patients still being alive but none from the surgical series being alive

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The reason for finding anaplastic squamous carcinoma in the specimen following radiotherapy is not yet certain It could result from the bronchial biopsy being taken from that small part of a tumor which is indeed oat-cell in nature while the predominant part of the tumor is squamous in nature It is well recognized that bronchial tumors may show several different histological patterns in any one tumor However the incidence did seem higher than such an explanation might support and therefore the possibility of change from oat cell to squamous cell appearance as a result of the radiotherapy was considered

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Since oral contraceptive use becomes less common with increasing age risk ratios were age standardized[2] (Table I) The association between venous thromboembolism and oral contraceptive use is highly significant. Duration of use did not influence the risk. The results of other case-control studies are similar [3-5] Because idiopathic venous thromboembolism is a relatively rare event the risk may not become apparent in prospective studies [6] Enhancement of coagulability induced by oral contraceptives[7] probably explains the association with venous thromboembolism as well as other thromboembolic disorders

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childbearing age[8] It is possible that hormonal differences account for the increased prevalence of the disease in women and that oral contraceptives potentiate the risk

Benign breast tumors are negatively associated with oral contraceptive use (Table I) Similar findings are reported by Vessey and associates.[9] There was no association either positive or negative of oral contraceptive use with newly diagnosed breast cancer although the number of cases in our study (23) was too small to allow statistical comparison The data suggest that oral contraceptives are "protective" against the development of benign breast tumors Since patients with benign tumors appear to be at risk to develop subsequent malignant breast disease[10] the protective effect of oral contraceptives might also extend to breast cancer

The associations reported in this study are not likely to be due to chance The findings are not explained by differences in age race hospital marital status parity or cigarette smoking We doubt that the results are significantly influenced by bias on the part of nurse monitors or admitting physicians The study documents associations—positive and negative—between oral contraceptive use and three important disease states Furthermore it demonstrates the value of the case control method in epidemiologic research

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Keep legs up

It is well known that arteriosclerotic obliterative arteritis with gangrene occurs frequently in the feet and legs but is rare in the arms and hands The feet and legs of many people with this disease must be amputated but extremely rarely if ever is amputation necessary for this disease in the arms and hands It is also known that arteriosclerosis is a disease of high pressure vessels and not of low pressure vessels even though the same blood with all its chemical ingredients flows through all vessels[1] Intraluminal pressure is therefore an important factor that predisposes to arteriosclerosis The higher the arterial blood pressure the more severe the associated arteriosclerosis tends to be Furthermore it is known that the pressure in the vessels of the feet and legs becomes considerably higher upon standing due to the force of gravity[2] and is lower with the feet and legs at heart level Placing the feet at heart level can be done as a preventive measure by lying down frequently during the day using footrests reclining chairs rockers and couches lying on the floor and even putting feet on the desk in the office This practice is certainly beneficial for normal people who wish to prevent or delay arteriosclerosis of the legs and for patients with impairment of arterial blood flow Keeping the feet up at heart level also assists venous return[2] and further reduces arterial blood pressure Standing still frequently and for long periods of time impairs venous return and in turn increases the pressure head which the arterial flow must overcome Walking and contracting the leg muscles pumps blood back to the heart[2] and assists arterial flow by reducing vis a tergo Arteries of the legs are prone to obliterative arteriosclerotic endarteritis and anything that reduces arterial blood pressure cannot be injurious but certainly could be beneficial The peculiarities of the vessels and circulation to the legs and feet have been described previously in detail[2] With quiet standing and with the full effects of gravity capillary pressure in the toes and feet must exceed the pressure in the ascending aorta Keeping the legs and feet up could reduce the degree of arteriosclerosis in the lower extremities

Keep the legs and feet at heart level

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Cardiac tamponade

To the Editor

We enjoyed the article Cardiac tamponade Report of a case after insertion of transvenous endocardial electrode (AM HEART J 88.88 1974) After Dr Kalloor [2] we think we may mention briefly two personal observations and put for ward a few remarks on the problem of hemopericardium following the insertion of an endocardiac electrode

In the course of some 750 insertions of temporary or per manent electrodes, we noted two cases of hemopericardium with cardiac tamponade The cases were first, a 59 year old man, and second, a 64 year old woman They suffered many Stokes Adams accidents Both had a temporary electrode urgently inserted through the left arm (median basilic vein) a bipolar electrode with a stylet in the first case and without a stylet in the other

Cardiac tamponade (the full picture occurred in each case with sweating dyspnea, drop in blood pressure venous turgescence paradoxical pulse and tachycardia) happened suddenly in the course of the insertion as far as the first pa tient was concerned. On the contrary it appeared progres sively in a few hours in the second patient Each time the in sertion of the electrode had been very difficult and many at tempts had been necessary The immediate evolution was favorable in a few hours with medical treatment in both cases and it was not necessary to proceed to urgent puncture of the pericardium. The first case was surgically controlled during the insertion of permanent epicardial electrodes There was a hemopericardium of about 100 c c The second patient left the ward in good health three weeks later but was lost sight of later on.

Here are the three points we should like to comment on

1 *Frequency of these accidents.* They are in fact considered exceptional. We can find the figure 0.21 per cent in our series of right endoventricular electrodes. And also in a series of 104 well studied and recently reported cases of hemopericar dium [1] we can find only five cases, one of them following the insertion of an electrode straight through the chest. Yet we think two facts must be stressed. A On the one hand when the insertion of a right hand side electrode is done with a stylet pushed right to its extremity it is easy to get into the pericardium (the diagnosis is based on the existence of high threshold and on the aspect of endocardial ECG and very often achieve an electrostimulation of the left ventricle) B On the other hand, while inserting a permanent stimulating electrode it is not rare to see a sudden and brief drop in blood pressure with fainting and sweating (4 cases out of a recent series of 260 observations[3]) independent of all vagal reaction. In such cases we can t rule out the existence of a break in the myocardial wall.

2 *The causes of these accidents.* As this happened in our two observations, this accident is probably the result of ag gressive handling of the right ventricular wall during a diffi cult insertion. That is why we try to insert our electrodes straight from the right auricle towards the pulmonary artery with the help of a curved stylet and without any propping against the wall, then associating a progressive backing movement and a clockwise rotation of the electrode so that we can slip it directly from the pulmonary infundibulum leaving the extremity of the electrode free of stylet for 2 or 3 cm.

3 *Evolution and treatment.* The systematic surgical evacuation does not seem indispensable when the immediate medical evolution is satisfactory because a small effusion happening in a few seconds can provoke a dramatic but reversible state

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3 Marsaud, G L entraînement électrosystolique au long cours (260 cas) Medical thesis, Limoges, 1974
4 Monassier J P Electrostimulation cardiaque tem poraire (163 observations) Medical thesis Limoges 1972

Reply

To the Editor

I thank Dr J P Monassier for his letter concerning my paper Cardiac tamponade which appeared in the JOUR NAL for July 1974

One of the reasons for writing up the single case of cardiac tamponade was to draw attention to the fact that surgical decompression of pericardium in acute cardiac tamponade is a very effective method of treatment and prevents all the se quelae and complications of the low output state which is bound to last for varying periods with non surgical treat ment Small amounts of blood in the pericardium may not in terfere with function and may be a welcome safeguard against further tamponade by obliterating the pericardial cavity

The fainting and sweating episodes which occur often under local anesthesia do not seem to be a problem when the procedure is being done under general anaesthesia[1]

A thoracotomy could be avoided if necessary by approach ing the pericardial cavity from below after excising the xiphoid process of sternum This is an excellent route for drainage but affords only a limited exposure in case suturing is necessary

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A method to ensure a normal distal pulse after brachial arteriotomy

To the Editor

Brachial arteriotomy for coronary arteriography and left heart catheterization had in our previous experience been as

sociated with a significant number of absent distal pulses.

For the last three years a bolus injection of heparin 10 000 to 15 000 units* has been given into the ascending aorta before arteriography is commenced with additional amounts given if the catheter remains in the artery over one hour

Other investigators may be interested to learn that over 500 brachial arteriotomies have been managed in this way and radial pulses at the end of the procedure and subsequently have always been present.

Furthermore we have found no need to reverse the heparin effect at the end of the procedure as subsequent hemorrhage has been absent or trivial and no more than before heparin was used in this way

The arteriotomy is closed with an adventitial 5/0 Tevdek II purse string suture placed in position before the arteriotomy is made A pressure bandage has always been applied and left in situ for 24 hours after the procedure

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*118 Units of heparin (Pularin) is equivalent to 1 mg

Book reviews

The Normal Apexcardiogram By Jos L. Willems, Brussels 1973 Arscia Uitgaven N V., 305 pages

Willems thoroughly reviews the subject of apexcardiography The monograph includes discussions of history methodology physiologic and hemodynamic relationships to the recordings applications in the evaluation of cardiac function, and its application to the practice of cardiology The book should be of special value to beginners who wish to learn the subject of apexcardiography The tracings illustrated are well selected and the bibliography is extensive This is a valuable addition to the medical literature

Hemodynamic Monitoring in a Coronary Intensive Care Unit Edited by Richard O Russel, M.D and Charles E. Rackley M D New York 1974 Futura Publishing Co 284 pages

As indicated by the title of this book the contributors describe the problems of hemodynamic monitoring of the heart and circulation in the coronary care unit. The 12 chapters include discussions of equipment methods, electrical hazards maintenance of apparatus and the coronary care unit, techniques and procedures recording role of technologists, nurses and other assistants role of computers, and clinical applications interpretations and management Practically all of the contributors are from Birmingham Alabama and are involved in the Myocardial Infarction Research Unit Program The discussions and material presented are good. Important illustrations of the use of hemodynamic monitoring and the considerations necessary for the application of such monitoring to patient care in the C.C.U are included in the book. This application not only presents the practice in Birmingham but also reviews clearly the principle of hemodynamic monitoring for beginners who can profit from this publication.

Emergency Care—Assessment and Intervention Edited by Carmen Warner Sproul and Patrick J Mullaney St. Louis 1974 The C V Mosby Company 406 pages

This book like many others on this and related subjects reviews the clinical considerations of emergency care The contributors are many and the subjects considered are the common ones Legal considerations are included among the problems Cardiovascular emergencies constitute a part of the book but psychiatric emergencies burns poisoning insect and reptile bites and other subjects constitute the major considerations This is a good review of emergency management as practiced in the present day emergency rooms of hospitals This is a practical book which should be available in the library of all emergency rooms

Cardiac Catheterization and Angiography Edited by William Grossman, M D Philadelphia 1974 Lea & Febiger 339 pages, 152 illustrations Price $24 50

Grossman has edited this book which should interest all cardiologists and all physicians who perform cardiac catheterization There really is nothing especially unique presented in this book However the beginner will find this a clear and practical source for study Those involved in the catheterization laboratories will learn the concept of the various contributors who discuss technic interpretation of recordings indications for catheterization and clinical application. The illustrations of apparatus simple line drawings of actual recordings are well selected. This is a useful interesting and valuable contribution to the literature related to cardiology

Books received

The Dictionary of Sodium Fats and Cholesterol By Barbara Kraus New York 1974 Grosset & Dunlap Inc 366 pp Price $9 95

The Dictionary of Calories and Carbohydrates By Barbara Kraus New York 1973 Grosset & Dunlap Inc 388 pp Price $8 95

Problem Oriented Medical Record Concepts By Richard E Easton, M D M P H Englewood Cliffs N J 1974 Appleton Century Crofts Inc 158 pp Price $9 95

Disseminated Intravascular Coagulation in Man. By J D Minna S J Robboy and R W Colman, Springfield, Ill. 1974 Charles C Thomas Publisher 207 pp

Announcements

Seminar on the hypertensive patient

The University of Texas Health Science Center at Houston Division of Continuing Education in collaboration with Baylor College of Medicine The University of Texas Medical Branch at Galveston and The University of Texas Medical School at Houston presents a seminar entitled New developments in the management of the hypertensive patient to be held on April 24 1975 at the Marriott Motor Hotel Houston Texas Details of the office management of the hypertensive patient will be discussed including the workup of the patient and the use of conventional antihypertensive agents New agents such as propranolol (*Inderal*) clonidine (*Catapres*) and diazoxide (*Hyperstat*) will be reviewed in detail Adverse effects of antihypertensive agents will be discussed and special attention will be given to new developments suggesting that reserpine may play a role in the development of breast cancer Both basic background material and practical points in the treatment of hypertensive patients will be stressed

Speakers will include Dr K D Bock of the University of Essen West Germany Dr Hershel Jick Boston Dr Norman Kaplan Dallas and Dr John Wallace New York City Program Coordinator will be Walter M Kirkendall M D Professor and Director Program in Internal Medicine The University of Texas Medical School at Houston For further information please write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Satellite seminar at Wingate Institute

The Center for the Study of Aging Inc and Wingate Institute for Physical Education and Sport announce A Satellite Seminar at Wingate Institute Israel prior to the Tenth International Congress of Gerontology on Physical Exercise and Activity for the Aging to be held on June 19 to June 21 1975 Scientific papers are invited The program includes invited speakers panels workshops and visits to rehabilitation facilities Registration is limited to professional and allied personnel in medicine physical education sports gerontology and rehabilitation Cooperating agencies include the President s Council on Physical Fitness and Sports the National Graduate University and the National Council on the Aging Inc For further information on the submission of papers and on registration please write (*For United States North and South America*) Raymond Harris M D President Center for the Study of Aging Inc 706 Madison Ave Albany N Y 12208 (*For Europe and Eastern hemisphere*) Dov Aldubi Ph D Scientific Director Wingate Institute for Physical Education and Sport Wingate Israel

American Heart Journal

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Editorial

What do the heart disease mortality statistics tell us?

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Cardiovascular diseases are responsible for half of all deaths in Northwestern Europe and North America Heart disease is by all odds the dominant cause of death in men under 65 Heart disease is also the leading cause of death among women under 65 even though in this broad age range female mortality rates from heart disease are only about a third of the male rates No other single factor is as significant as sex in heart disease mortality These facts are well known even to the public because of education and fund raising campaigns over the last several decades Since the 1950s billions of dollars have been spent by governmental and private agencies seeking control over this vast and complex public health problem What trends or clues of progress are suggested by the mortality data available from population studies and insurance statistics?

Essential to any consideration of this subject is the recognition that the term heart disease represents many diseases of the cardiovascular system While every clinician and medical scientist knows this because of the publicity given to heart attacks, the man in the street generally equates heart disease with coronary artery disease Even this condition may need to be seen as a more complex phenomenon Deaths from heart disease due to congenital defects rheumatic fever, and hypertension have decreased quite dramatically in the 1960 s, reflecting advances in surgical and medical management According to detailed studies performed by the Metropolitan Life Insurance company by Lew and Entmacher[1] for the white male population the mortality rate for rheumatic heart disease decreased 34 per cent However this form of heart disease accounts for less than 2 per cent of the total mortality Congenital heart disease dropped 22 per cent in the 1960s but is responsible for only 1 per cent of total heart mortality Hypertensive heart disease declined 29 per cent but represents only 4 per cent of all heart mortality *

On the other hand during this same period mortality from arteriosclerotic heart disease which includes coronary disease increased by 2 per cent among white males and 1 per cent among white females of all ages Since this form of heart disease accounts for five-sixths of the total mortality from heart disease among white males and three fourths among white females these losses more than offset the gains in the other forms of heart disease Thus in the 1960 s for the United States population the balance sheet for heart disease mortality showed virtually no gain

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*Between 1960 and 1967 the codes for the cardiovascular causes of death remained unchanged so that valid comparison can be made between the death rates from these diseases reported in these years

This is disappointing in light of the vast resources thrown into this battle in the last decade On the other hand the problem of arteriosclerotic heart disease is extremely complex Warren[2] suggests that coronary artery disease be thought of as a group of major syndromes Each is a manifestation of the underlying arteriosclerotic process and each responds differently, perhaps, to risk factors Modifying lifestyles and risk factors—if these be etiologic factors—is a formidable task In spite of some enthusiastic claims, assessment of the outcome may require a decade or more Management of acute heart attacks while vastly improved needs further expansion, especially to include health education of the public so that an acute attack is recognized earlier and emergency measures can be administered by trained laymen even before the arrival of the ambulance

In seeking evidence of the value of programs of primary and secondary prevention which have been applied during the past decade mortality studies by socio economic class provide clues There is a growing body of facts which shows a close relationship between higher economic and education attainment and lower mortality from cardiovascular disease

In a country as large and heterogenous as the United States the mortality rates of the total population can mask evidence of mortality trends Comparisons among states and countries with significantly different standards of living reveal contrasts in cardiovascular mortality Analysis of data by education and social class because of the influence on lifestyles also reveals important differences For example, the mortality studies of Guralnick,[3] in 1950 among men 20 to 64 years of age in nine major occupational groups showed generally lower heart disease death rates for occupations in the higher socio economic classes Kitagawa and Hauser[4] in 1960 showed that higher education was significantly related to lower mortality from heart disease as well as for all causes The Metropolitan Insurance Company recently conducted a variety of studies on its insured populations and on prominent and successful professional and businessmen which sheds further light on these factors[5-7] For example persons insured with the Metropolitan Life Insurance Company under standard ordinary policies had a substantially lower mortality rate from heart diseases than did those persons insured under industrial policies The two categories may be considered to represent broadly different socio economic strata Standard ordinary policyholders are drawn chiefly from urban middle and well to do classes while industrial policyholders are mainly members of urban wage earning families in the lower income brackets Our statisticians have also conducted studies of mortality experience of Metropolitan Life Insurance employees and employees of several other large employers Altogether, these represent several hundred thousand persons and from five to fifteen years observation In all cases, executive and administrative personnel representing the highest salary groups had the lowest mortality from heart disease Even among those in the highest corporate levels where coronary disease and mortality is lowest, there were appreciably lower rates among college graduates than among noncollege men

In Great Britain[8] where mortality studies have been related to social class for several generations the most recent report indicates that the highest classes have the lowest mortality rate from heart disease The experience for married women follows the pattern of their husbands

A comprehensive review of the follow up studies of men who survived a first myocardial infarction indicates that persons in the higher socio economic segments of the population have a distinctly better record of survival after a year or two have elapsed following the acute episode[9] A similar long term study of Hrubec and Zukel[10] relating to the survival of well authenticated cases of myocardial infarction suffered while in the Armed Forces of the United States during World War II shows clearly that physicians and professional men with a college education have had a better survival record than men in other occupations or with lesser education attainments

Is this lower mortality due to better health practices and easier access to first rate medical care for the better educated and the more affluent? Are there other factors which account for these differences? Are the mortality differentials associated with different manifestations of coronary artery disease? What is the relative importance of socio economic factors vs hypertension smoking elevated cholesterol and obesity in primary and secondary prevention programs?

While socio economic factors appear to have a distinct influence on the mortality from coronary artery disease epidemiologic studies point up the importance of hypertension smoking elevated cholesterol and obesity These factors cut across socio economic classes and thus complicate the study of their relative importance in programs of primary and secondary prevention For example there is evidence that moderation in living habits as exemplified by a state such as Utah with its relatively homogenous population predisposes to low mortality Stressful living often manifested by excessive cigarette smoking by overeating and by hypertension may be the catalyst that precipitates acute myocardial infarction The differences between individuals in responding to various stresses lend support to the concept of the coronary prone personality Much speculation and an increasing amount of research have been devoted to evaluating the importance of psychological factors in cardiovascular disease Brenner[1] suggests that a significant proportion of the population is subject to major stresses that originate in threats to their economic status His studies show clearly that economic downturns are associated with increased mortality from heart disease and conversely that heart disease tends to decrease during economic upturns In countries where the social motivation to achieve material success is very strong economic depressions obviously constitute highly stressful situations for large segments of the population The present international energy crisis and its attendant economic crunch provides an opportunity to test this thesis

The etiology of coronary artery disease undoubtedly involves numerous factors and we need more objective studies to determine their relative importance in primary and secondary prevention As medicine moves toward more involvement with Health Maintenance Organizations and other approaches which seek to apply risk concepts to prospective medicine and health knowledge to the prevention minimizing of disability and life saving the acquisition of reliable data on the life history of heart diseases must have the highest priority In the future such research is essential for proper evaluation of society s enormous financial commitment in the struggle against cardiovascular disease

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Much of the data and the discussion of risk factors in this editorial come from a paper prepared by Lew and Entmacher for the Skandia International Symposium Stockholm Sweden 1972 on the mortality in early phases of cardiovascular disease

This is disappointing in light of the vast resources thrown into this battle in the last decade On the other hand, the problem of arteriosclerotic heart disease is extremely complex Warren[2] suggests that coronary artery disease be thought of as a group of major syndromes Each is a manifestation of the underlying arteriosclerotic process and each responds differently perhaps, to risk factors Modifying lifestyles and risk factors—if these be etiologic factors—is a formidable task In spite of some enthusiastic claims, assessment of the outcome may require a decade or more Management of acute heart attacks, while vastly improved needs further expansion, especially to include health education of the public so that an acute attack is recognized earlier and emergency measures can be administered by trained laymen even before the arrival of the ambulance

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In a country as large and heterogenous as the United States, the mortality rates of the total population can mask evidence of mortality trends Comparisons among states and countries with significantly different standards of living reveal contrasts in cardiovascular mortality Analysis of data by education and social class because of the influence on lifestyles also reveals important differences For example the mortality studies of Guralnick,[3] in 1950, among men 20 to 64 years of age in nine major occupational groups showed generally lower heart disease death rates for occupations in the higher socio economic classes Kitagawa and Hauser,[4] in 1960 showed that higher education was significantly related to lower mortality from heart disease as well as for all causes The Metropolitan Insurance Company recently conducted a variety of studies on its insured populations and on prominent and successful professional and businessmen which sheds further light on these factors[5-7] For example, persons insured with the Metropolitan Life Insurance Company under standard ordinary policies had a substantially lower mortality rate from heart diseases than did those persons insured under industrial policies The two categories may be considered to represent broadly different socio economic strata Standard ordinary policyholders are drawn chiefly from urban middle and well to do classes while industrial policyholders are mainly members of urban wage earning families in the lower income brackets Our statisticians have also conducted studies of mortality experience of Metropolitan Life Insurance employees and employees of several other large employers Altogether these represent several hundred thousand persons and from five to fifteen years observation In all cases executive and administrative personnel representing the highest salary groups had the lowest mortality from heart disease Even among those in the highest corporate levels, where coronary disease and mortality is lowest, there were appreciably lower rates among college graduates than among noncollege men

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Lidocaine 100 mg was injected intravenously within exactly 20 seconds in all patients Blood was sampled from the femoral artery before and 10 20 30 45 60 90 120 and 180 seconds after the beginning of the injection Continuous recordings were made at a paper speed of 100 mm per second

The study of the acute effects of an intravenous bolus injection being completed all measurements were repeated 7 to 10 minutes after this injection and venous plasma samples were obtained to verify therapeutic drug levels

Intramuscular injection of 250 mg of lidocaine in the lateral muscles of the thigh preceded the intravenous injection in 14 patients In these patients measurements were repeated 10 and 20 minutes after the intramuscular injection, at which times plasma samples were again obtained

Plasma lidocaine was determined by gas liquid chromatography and expressed as micrograms per milliliter (therapeutic range 2 to 6 μg per milliliter)

Definition of terms

PA interval time between the onset of the P wave in the standard leads or the high atrial ECG and the onset of the P wave in the low atrial electrogram as recorded on the His bundle ECG (normal 0 to 40 msec)

AH interval time between the onset of the P wave on the His bundle ECG and the onset of the His spike (normal 60 to 140 msec)

HV interval time between the onset of the His spike and the onset of the QRS complex in the standard leads (normal 30 to 55 msec)

HS interval time between the onset of the His spike and the end of the QRS complex in the standard leads (normal 100 to 145 msec)

Pooled AH intervals sum in milliseconds of the AH times at each driven atrial rate with 1 1 or 2 1 A V conduction

Wenckebach point (W P) the highest driven atrial rate permitting 1 1 conduction In patients with the Wenckebach phenomenon while in sinus rhythm the highest driven atrial rate permitting 2 1 conduction was taken as W P

SART the interval in milliseconds between the last pacemaker pike and the first spontaneous P wave after abruptly turning off the external pacemaker 20 seconds after atrial pacing at a rate of 120 per minute

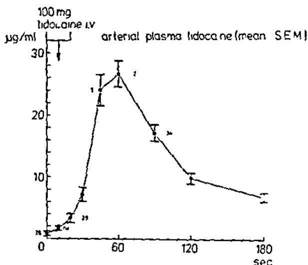


Fig 1 Arterial plasma lidocaine levels (mean ± S E M) after intravenous bolus injection of 100 mg of lidocaine Therapeutic range 2 to 6 μg per milliliter

Effective refractory period of the atrium (ERP) the longest S S_2 interval at which S_2 does not propagate into the atrium

Effective refractory period of the A V node (ERP) the longest A_1 A_2 interval at which A_2 fails to reach the His bundle

Functional refractory period of the A V node (FRP) the shortest interval between H and H_2 both of which are conducted from the atrium

Effective refractory period of the His Purkinje system (ERP_{hp}) the longest H H_2 interval at which H_2 fails to conduct to the ventricles

Relative refractory period of the His Purkinje System (RRP_{hp}) the longest H H_2 interval at which H conducts to the ventricles with a longer HV interval and/or with an aberrant QRS complex

Results

In Table I the pertinent clinical data and the conduction intervals during control recordings are listed together with the Wenckebach point (WP) pooled AH times and pooled HV times before and after lidocaine administration

To establish whether the subcutaneous anesthesia with 80 to 100 mg of lidocaine at the site of catheter introduction could influence the control recordings venous plasma samples were obtained in this period from 30 patients In 24 patients no lidocaine could be detected and in the remaining

Clinical communications

Effects of lidocaine on impulse formation and conduction defects in man

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Lidocaine is probably the most widely used anti arrhythmic drug in the treatment and prevention of ventricular arrhythmias in acute myocardial infarction and its use has been demonstrated to reduce hospital mortality[1-15] Apart from its well known side effects on the central nervous system, serious conduction disturbances and cardiac arrest have been reported in the literature[9-15] Although the drug seems to have little influence on A V nodal and intraventricular conduction in patients with intact A V conduction,[16,17] little is known of its effect on already compromised A V conduction and impulse formation and the available data are contradictory[19-21] We therefore studied the electrophysiologic effects of lidocaine in 39 patients with pre existent impulse formation and conduction defects and correlated these with plasma lidocaine levels Ten patients with acute myocardial infarction were included in the study because ventricular arrhythmias caused by this disease form the main indication for the use of this drug

Material and methods

Studies were carried out in 39 patients after informed consent was obtained Two patients were studied twice because of changed A V conduction Ten patients were studied within three days after the onset of acute myocardial infarction Cardiac drugs were withheld at least 48 hours before the study No patient was in overt heart failure or suffered from liver disease

After analysis of the His bundle recordings, the patients could be assigned to one of the following groups (Table I) I patients with conduction delay in or below the level of the His bundle (17), II patients with conduction delay proximal to the His bundle (6) III patients with conduction delay both proximal and distal to the His bundle (9), and IV patients with sinus node malfunction (9) These patients all had a history of syncope and/or palpitations together with electrocardiographic evidence of sinus node malfunction (sinus bradyarrhythmia, sinus arrest sino atrial block and the bradytachycardia syndrome)

Using the Seldinger technique two catheters were introduced in the right femoral vein a tripolar catheter No 7, was positioned against the lateral wall of the right atrium and a bipolar electrode wire with electrodes 1 cm apart in the His bundle region as described by Scherlag and co workers[22] Standard Leads I II, and III, a unipolar high atrial electrocardiogram (ECG), and a His bundle ECG were recorded on an 8 channel Elema at a paper speed of 100 mm per second In 15 patients, refractory periods were measured using the extra stimulus technique with a modified Medtronic external pulse generator (No 5837) delivering an atrial premature beat with a variable coupling interval after every eighth beat of the basic paced cycle at twice diastolic threshold

In 34 patients the atrium was driven at increasing rates until A V conduction became incomplete or a rate of 180 to 200 per minute was reached

In 19 patients, the sino atrial recovery time (SART) was measured when the pacemaker was abruptly turned off after atrial pacing at a rate of 120 per minute during 20 seconds The mean of five determinations was taken as SART

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Heart rate	*PA*	*AH*	*HV*	*HS*	*WP*	*WP'*	*Pooled AH*	*Pooled AH*	*Pooled HV*	*Pooled HV'*
0	0	110	70	?10	–	–	–	–	–	–
89	20	90	30	180	>1.0	>150	.95	590	205	195
66	0	150	40	180	120	130	1 090	970	?00	200
75	0	105	40	1 5/195	>160	>160	1 095	1 055	375	.75
80	40	60	60	200	150	150	755	785	1?5	110
10?	10	90	65	240	140	140	805	825	3?5	325
58	?0	1?0	40	1.0	90	100	1 065	945	200	200
6?	?0	95	35	135/175	160	140	1 100	1 2?5	300	270
6?	30	130	60	195	130	–	–	–	–	–
86	?0	100	45	130	170	1.0	1 445	1 350	315	315
91	20	80	60	230	>1.0	>1.0	830	8 0	4?0	480
1?0	20	60	60	200	>190	>190	.85	580	4?0	4?0
94	0	90	60	190	>200	>?00	745	7 0	425	430
104	20	140	60	160	180	1.0	1 ?00	1 85	490	480
87	20	120	?0	210	150	150	1 040	1,090	395	390
83	20	140	70	230	160	160	1 735	1 ?9.	630	630
30	–	–	–	–	–	–	–	–	–	–
63	15	5 5/645	50	150	–	–	–	–	–	–
56	10	160	40	120	80	70	400	410	80	80
88	?0	?30/6.0	40	140	130	140	455	380	80	80
97	20	80/180	30	110	160	160	1 006	1 040	245	245
.0	0	385/415	35	145	110	110	1 075	1 075	105	105
44	15	–	40	100	–	–	–	–	–	–
8	20	170	40	130/160	140	120	1 480	1,325	280	280
51	40	?10	60	165	90	90	? 3?5	2 335	495	495
53	10	300	50	200	80	80	960	980	1.0	150
?8	20	?00	55	?00	1 0	1.0	455	500	110	110
56	10	190	65	??5	130	130	2 130	1 660	5?0	5?0
9?	20	155	40	210	110	130	1 7.5	1 665	3.0	360
74	40	160	80	250	160	160	1,08.	985	480	480
88	30	165	65	255	160	140	390	395	195	19
4?	–	–	40/60	150/180	–	–	–	–	–	–
44 ?9	0	130	40	120	130	130	1 150	1 165	235	230
55-80	40	9.	35	110	160	140	795	830	280	280
4..1	10	105	40	130	110	100	1 085	1 0?5	240	240
80	10	140	60	?10	>180	>180	1 50	1 9?0	540	540
54	20	85	50	?10	160	160	2 340	? 390	550	550
5	30	155	55	135	100	100	1 725	1 62.	440	440
39-120	40	110/1?0	45	1?0	–	–	–	–	–	–
5	20	80	5.	145	130	130	895	9.0	550	550
1	30	9	30	1?0	180	180	1,29	1,300	300	300

LAH = left nterio hemiblock,
PAC = premature atrial contraction,
PVC = prem t re ventricular contraction

WP defi ed as h ghest trial rate permitting ? 1 A V conduction in patients with the Wen k bach phenomenon during sinus rhythm

Table I

		Age	Sex	Clinical characteristics	Type of conduction disturbance
Group I conduction disturbances in or distal to the His bundle	1 Ve	67	M	Syncope	RBBB LBBB Mobitz Type II
	2 Fi	4[illegible]	M	Recent anterior infarction	RBBB
	3 Zw	[illegible]8	M	Asymptomatic	RBBB LAH
	4 Hu	[illegible]	M	Recent inferior infarction	Incomplete and complete RBBB
	5 Co	81	M	Asymptomatic	LBBB Mobitz Type II
	6 No	72	M	Recent anterior infarction	RBBB LAH
	7 Ja	[illegible]2	M	Old anterior infarction	RBBB LAH
	8 Mo	[illegible]9	M	Angina pectoris dizziness	Intermittent RBBB
	9 Fe	81	M	Syncope	RBBB Mobitz Type II
	10 Ko	81	F	Adams Stokes attacks	Total heart block Mobitz Type II
	11 Am	[illegible]9	M	Recent anterior infarction	RBBB LAH Total heart block
	12 Kr	76	F	Recent anterior infarction	RBBB LAH Total heart block
	13 Me	6[illegible]	F	Asymptomatic	RBBB LAH 2 1 Mobitz Type II
	14 Ns	66	F	Syncope	2 1 3 1 A V block Total heart block
	15 Ms	[illegible]	M	Recent inferior infarction	LBBB
	16 Oo	77	M	Adams Stokes attacks	LBBB
	17 Ie	71	F	Heart failure	Atrial fibrillation Total heart block LBBB
Group II Conduction disturbances proximal to the His bundle	18 B	19	M	Old inferior infarction	First degree A V block Wenckebach
	19 He	77	M	Recent inferior infarction	First degree A V block
	20 M	71	F	Recent inferior infarction	Wenckebach
	21 Bo	[illegible]1	M	Recent inferior infarction	Wenckebach
	22 Wa	[illegible]	M	Recent inferior infarction	Wenckebach
	23 Bu	4[illegible]	F	Adams Stokes attacks	Total heart block
Group III Conduction disturbances proximal and distal to the His bundle	19 He	[illegible]	M	Old inferior infarction	First degree A V block RBBB
	24 Ro	7[illegible]	M	Old inferior infarction	First degree A V block Intraventricular conduction delay
	25 Cd	70	M	Syncope	RBBB LAH First degree A V block
	26 Se	8[illegible]	M	Adams Stokes attack	LBBB Wenckebach
	16 Oo	7[illegible]	M	Syncope	LBBB First degree A V block
	27 Kor	6[illegible]	F	Syncope	LBBB First degree A V block Wenckebach
	28 Br	60	M	Old inferior infarction	RBBB LAH First degree A V block Wenckebach
	29 Cm	[illegible]5	M	Dizziness	RBBB LAH First-degree A V block Wenckebach
	30 W	50	M	Asymptomatic	Atrial flutter Total heart block LBBB
Group IV Sinus node malfunction	31 Ho	71	F	Old inferior infarction	Sinus bradycardia PAC PVC
	32 Ve	77	F	Adams Stokes attack	Sinus bradycardia Sinus arrest
	33 Du	48	F	Bradytachycardia syndrome	Sinus bradycardia PAC Atrial fibrillation
	34 Wi	41	F	Syncope	Sinus arrest Atrial fibrillation LBBB
	35 H	73	F	Dizziness	Sinus bradycardia Sinus arrest LBBB
	36 Vl	7[illegible]	F	Dizziness	Sinus arrest Atrial quiescence
	37 Ga	83	F	Syncope heart failure	Sinus bradycardia Sinus tachycardia LBBB
	38 Bos	[illegible]9	M	Syncope	Hypersensitive carotid sinus
	39 Di	78	F	Old inferior infarction	Sinus arrest

PA = PA interval in milliseconds
AH = AH interval in milliseconds
HV = HV interval in milliseconds
HS = HS interval in milliseconds
WI = Wenckebach point before lidocaine
WP = Wenckebach point after lidocaine

pooled AH = pooled AH times before lidocaine
pooled AH = pooled AH times after lidocaine
pooled HV = pooled HV times before lidocaine
pooled HV = pooled HV times after lidocaine
RBBB = right bundle branch block
LBBB = left bundle branch block

Heart rate	PA	AH	HV	HS	WP	WP*	Pooled AH	Pooled AH*	Pooled HV	Pooled HV*
[illegible]0	0	110	[illegible]0	210	–	–	–	–	–	–
89	20	90	30	180	>150	>150	595	[illegible]90	[illegible]05	195
66	0	150	40	180	1[illegible]0	130	1 090	9[illegible]0	200	200
[illegible]	0	105	40	1[illegible]5/195	>160	>160	1 095	1 055	3[illegible]5	375
80	40	60	60	200	150	150	755	78[illegible]	1[illegible]5	110
10[illegible]	10	90	65	[illegible]40	140	140	805	825	325	325
58	20	1[illegible]0	40	170	90	100	1 065	945	200	200
6[illegible]	[illegible]0	[illegible]5	35	135/175	160	140	1 100	1 275	300	270
6[illegible]	30	130	60	195	130	–	–	–	–	–
86	20	100	45	130	1[illegible]0	1[illegible]0	1 445	1 350	315	315
91	20	80	60	230	>1[illegible]0	>1[illegible]0	830	8[illegible]0	480	480
120	[illegible]0	60	60	200	>190	>190	585	[illegible]80	4[illegible]0	420
94	0	90	60	190	>[illegible]00	>200	745	7[illegible]0	4[illegible]5	430
104	[illegible]0	140	60	160	180	1[illegible]0	1 [illegible]60	1 [illegible]85	490	480
8[illegible]	20	1[illegible]0	[illegible]0	210	150	150	1 040	1 090	395	390
83	[illegible]0	140	70	230	160	160	1 73[illegible]	1 [illegible]9[illegible]	630	630
30	–	–	–	–	–	–	–	–	–	–
63	15	[illegible]/645	50	150	–	–	–	–	–	–
[illegible]6	10	160	40	1[illegible]0	80	[illegible]0	400	410	80	80
68	[illegible]0	230/650	40	140	130	140	455	360	80	80
97	20	80/180	30	110	160	160	1 00[illegible]	1 040	245	245
[illegible]0	0	38[illegible]/415	35	145	110	110	1 075	1 075	105	105
44	15	–	40	100	–	–	–	–	–	–
8	20	1[illegible]0	40	130/160	140	120	1 480	1 325	280	280
51	40	210	60	165	90	90	2 325	2 33[illegible]	495	49[illegible]
[illegible]3	10	300	50	[illegible]00	80	80	960	980	150	150
8	20	[illegible]00	55	200	120	130	455	500	110	110
56	10	190	65	225	130	130	2 130	1 660	520	520
9[illegible]	[illegible]0	15[illegible]	40	210	110	130	1 7[illegible]5	1 665	360	360
4	40	160	80	2[illegible]0	160	160	1 085	985	480	480
68	30	165	65	[illegible]	160	140	390	395	195	195
4[illegible]	–	–	40/60	150/180	–	–	–	–	–	–
44-[illegible]9	0	1[illegible]0	40	120	130	130	1 150	1 165	23[illegible]	230
5[illegible]-80	40	95	35	110	160	140	[illegible]95	830	280	280
4[illegible]1	10	10[illegible]	40	130	110	100	1 085	1 025	240	240
80	10	140	60	[illegible]10	>180	>180	1 750	1 9[illegible]0	540	[illegible]40
54	20	8[illegible]	[illegible]0	[illegible]10	160	160	2 340	2 390	550	550
5	30	155	[illegible]5	13[illegible]	100	100	1 725	1 6[illegible]5	440	440
39-1[illegible]0	40	110/120	45	1[illegible]0	–	–	–	–	–	–
[illegible]5	20	80	55	145	130	130	89[illegible]	950	550	550
1	30	95	30	120	180	180	1,295	1 300	300	300

LAH = left anterior hemiblock,
PAC = premat re atrial contraction
PVC = premature ventricul r contraction

WP d fined as highest atrial rate perm tt ng 1 A V conduction in patients with the Wenckebach phenomen n during sinus rhythm

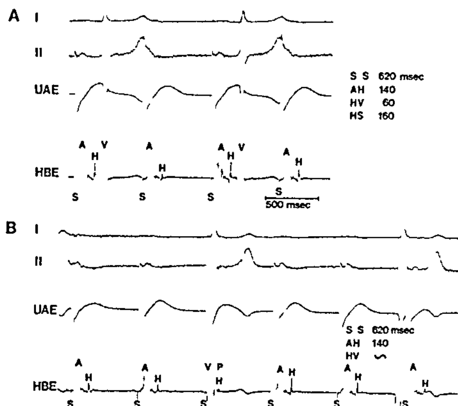


Fig 2 Patient No 14 Panel *A* shows a 2 1 Mobitz Type II block distal to the His bundle in the control period Panel *B* shows a complete heart block distal to the His bundle which existed from 57 to 75 seconds after the beginning of the intravenous bolus injection of 100 mg of lidocaine *UAE* unipolar atrial electrogram *HBE* His bundle electrogram *S* stimulus artifact *A* A wave on the UAE or HBF *H* His bundle deflection and V QRS complex

six patients, plasma levels ranged from 0 5 to 0 8 μg per milliliter and were well below the minimal therapeutic level of 2 0 μg per milliliter

Intravenous bolus administration of lidocaine Fig 1 shows the mean ± S E M of the arterial plasma lidocaine levels during and after an intravenous bolus of 100 mg of lidocaine Between 30 and 120 seconds after the beginning of the injection extremely high levels are found with a maximum of 26 6 μg per milliliter after 60 seconds The mean plasma level at time zero was 0 8 μg per milliliter, due to the preceding intramuscular injection of 250 mg of lidocaine in 14 patients This cannot explain the extreme levels at 60 seconds, because in 11 patients in whom no lidocaine was detectable at time zero the mean peak level at 60 seconds was 24 4 μg per milliliter

Conduction distal to the His bundle These toxic plasma lidocaine levels had a remarkable influence on intraventricular conduction in patients of Groups I and III Thus in seven out of 26 patients (all with conduction disturbances in or distal to the His bundle), infra His conduction deteriorated transiently In patient No 14, a 2 1 Mobitz Type II block progressed to total heart block distal to the His bundle (Fig 2) In two patients (Nos 1 and 5) with bilateral bundle branch block and 1 1 conduction a Mobitz Type II block appeared (Fig 3) In one patient (No 6) with RBBB and LAH one atrial impulse was blocked distal to the His bundle and in three other patients (Nos 4 8 and 30) with incomplete or intermittent bundle branch block the number of beats with complete block in one of the bundle branches increased See Fig 4 for example

In all these patients the progressive conduction defect distal to the His bundle occurred and disappeared between 30 and 200 seconds after the beginning of the intravenous bolus injection and thus coincided with peak plasma levels In the other patients in Groups I and III infra His conduction was stable even at the highest plasma lidocaine levels In the patients with normal intraventricular conduction the HV and HS interval were constant during and after intravenous lidocaine administration

Conduction proximal to the His bundle No

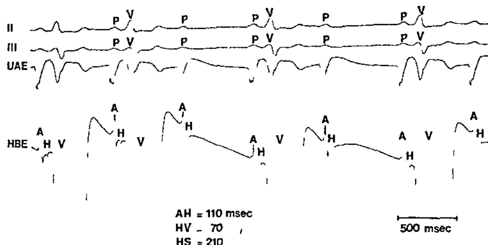


Fig 3 Patient No 1 This figure shows the transition of 1:1 conduction to 2:1 Mobitz Type II block occurring 30 seconds after the beginning of the intravenous bolus injection of 100 mg of lidocaine After 120 seconds 1:1 conduction returned

effect of lidocaine could be demonstrated on A V nodal conduction during intravenous injection even in the patients with high degrees of A V nodal conduction disturbances In one patient (No 19) who had 4:3 Wenckebach conduction in the control period 1:1 conduction with first degree A V block existed from 100 to 145 seconds after the beginning of intravenous lidocaine injection Because such improvement was not observed in any of the other patients we are inclined to ascribe this to spontaneous variation in autonomous nervous tone rather than to a direct effect of the drug In the three patients with total heart block lidocaine failed to influence the spontaneous firing rate of the escape focus In none of the patients who were in sinus rhythm were significant changes found in the sinus rate during and after intravenous lidocaine administration

Infra His conduction at therapeutic plasma lidocaine levels Changes of HV and HS intervals during sinus rhythm were seen in only one patient at therapeutic drug levels This patient (No 4) studied in the acute phase of inferior myocardial infarction had incomplete right bundle branch block in the control period With increasing plasma lidocaine levels the number of beats with complete RBBB increased as shown in Fig 4

Atrial pacing At therapeutic plasma lidocaine levels progressive intraventricular conduction delay became manifest in five out of 26 patients of

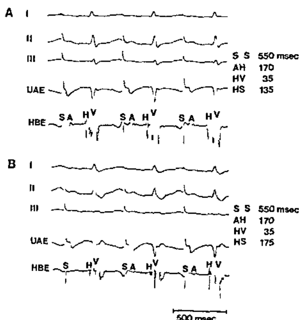


Fig 4 Patient No 8 Panel *A* shows 1:1 and normal intraventricular conduction in the control period Between 30 and 57 seconds after the beginning of the intravenous bolus injection of 100 mg of lidocaine a complete right bundle branch block (RBBB) existed (panel *B*) The HS interval increased from 135 to 175 msec and Lead I shows the typical deep S wave of RBBB

Groups I and III during atrial pacing Thus the Mobitz Type II point (in analogy of the WP the highest driven atrial rate permitting 1:1 conduction through the His Purkinje system) shifted from 150 to 110 in patient No 5 In patient No 10

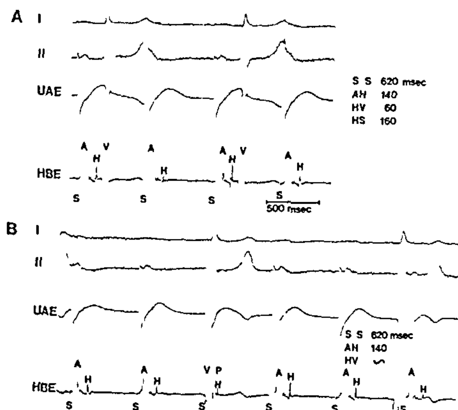


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Conduction proximal to the His bundle No

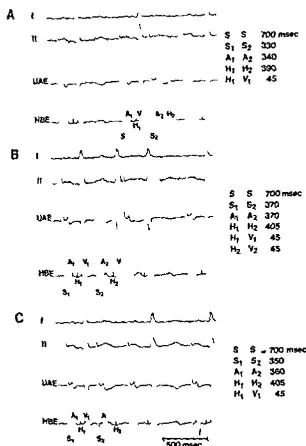


Fig 7 Patient No 10 Panel *A* shows the longest H H interval of 390 msec not propagating to the ventricles (ERP$_{HP}$) during the control period In panel *C* at a therapeutic plasma lidocaine level of 4 7 μg per milliliter the ERP$_{HP}$ has increased to 405 msec Panel *B* shows the same H H interval of 405 msec during control recordings at which H does reach the ventricles S S basic cycle length S S interval between the last stimulus artifact of the basic cycle and the extra stimulus A H V belong to the cycle caused by S and A H V

The RRP$_{HP}$ of patient No 8 increased from 530 to 5?? msec In patient No 14 who had 2 1 block distal to the His bundle 46 per cent of the P waves were conducted through the His Purkinje system during the control period while after lidocaine (plasma level 2 6 μg per milliliter) only 33 per cent were conducted at the identical paced atrial rate of 160 per minute

In none of the other patients of Groups I and III and in none of the patients with normal intraventricular conduction was any change in the infra His conduction seen at therapeutic plasma lidocaine levels The refractory periods of the His Purkinje system are listed in Table II

A V nodal conduction at therapeutic plasma lidocaine levels Pooled AH times at comparable paced atrial rates in the control period and at therapeutic lidocaine levels (mean 2 98 ± 0 31 S E M) are listed in Table I In Fig 8 pooled AH times after lidocaine are expressed as percentage of the pooled AH times in the control period (equals 100 per cent) The mean pooled AH times after lidocaine were 99 6 per cent of the control value (S D = 7 9) From these data it appears

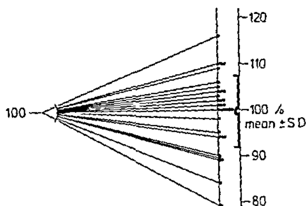


Fig 8 Pooled AH times at therapeutic lidocaine levels are expressed as percentage of the pooled AH intervals during control recordings (100 per cent) After lidocaine the mean pooled AH intervals were 99 6 ± 7 9 (S D) of the control values

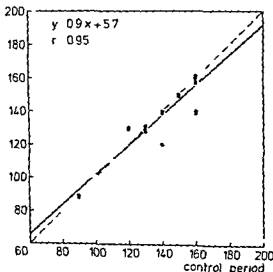


Fig 9 The highest driven atrial rate permitting 1 1 conduction (or 2 1 conduction in patients with the Wenckebach phenomenon during sinus rhythm) in the control period is plotted on the abscissa The Wenckebach point at therapeutic plasma lidocaine levels is plotted on the ordinate

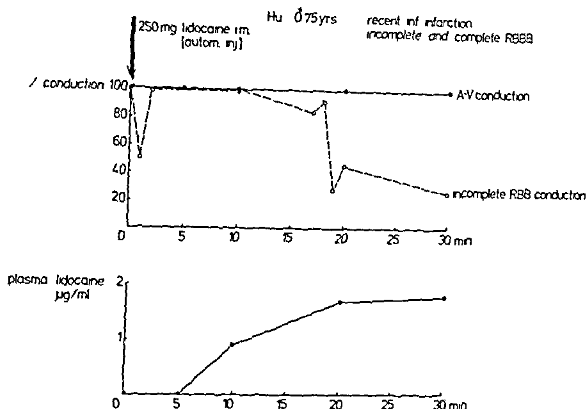


Fig 5 Patient No 4 The lower panel shows the plasma lidocaine levels after 250 mg of lidocaine intramuscularly with an automatic injection device The upper panel shows the percentage of conducted beats (solid line) With increasing plasma lidocaine levels the number of beats with complete right bundle branch (RBBB) increased and the percentage of beats with incomplete RBBB decreased (interrupted line)

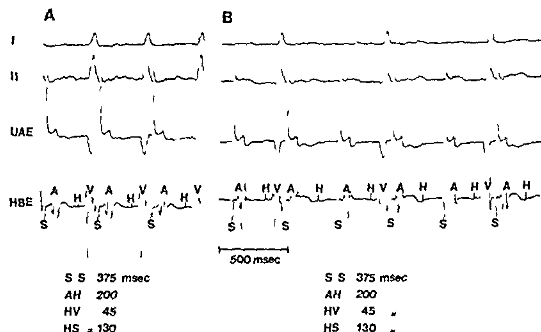


Fig 6 Patient No 10 Panel *A* shows 1 1 conduction at an atrial paced rate of 160 per minute (S S = 375 msec) At this same rate 2 1 Mobitz Type II block distal to the His bundle existed at a plasma lidocaine level of 4 7 µg per milliliter (panel *B*)

this point was reached at an atrial rate of 150 per minute (plasma lidocaine 4 7 µg per milliliter) while in the control period 1 1 conduction still existed at a rate of 170 per minute as shown in Fig 6 The ERP_{hp} increased from 390 to 405 msec and the RRP_{hp} from 390 to 410 msec (see Fig 7) In two patients (Nos 4 and 8) with incomplete bundle branch block, the number of beats with complete bundle branch block increased after lidocaine at each driven atrial rate

RRP		*Cycle length (msec)*	*Plasma lidocaine*
Before	*After*		
–	–	810	0 6
–	–	750	[illegible] 2
–	–	900	1 1
390	410	700	4 7
–	–	650	2 4
–	–	450	4 9
–	–	560	–
–	–	6[illegible]0	[illegible] 6
490	–	600	7 0
–	–	550	[illegible] 3
–	–	860	3 8
–	–	680	4 5
–	–	800	3 4
–	–	500	6 0
–	–	00	3 4

atrial pacing compared to control values in any patient.

Considering the ten patients with acute myocardial infarction, it appears that these patients did not differ from the others in respect to the occurrence of progressive conduction delay due to lidocaine. Thus, of 26 patients in Groups I and III, six (28 per cent) had a recent myocardial infarction. Of the total of eight patients who showed decremental conduction after lidocaine, two (25 per cent) had an acute myocardial infarction.

Discussion

Many authors advise against the use of lidocaine in the presence of conduction or impulse formation disturbances. This is based on reports in the literature of adverse reactions to lidocaine after intravenous administration. Thus, patients were reported who developed sino-atrial arrest after lidocaine by Lippestad and Forfang, Jeresaty, Kahn, and Landry, and Wood.

Jewitt, Kishon, and Thomas[9] described a patient with sinus bradycardia and hypotension after lidocaine. Gianelly and co-workers[11] reported a patient with second degree A-V block and myocardial infarction who developed total heart block after lidocaine. No mention of the site of the block was made. Flensted-Jensen and Sandøe[6] reported a patient who died in asystole after 150 mg. of lidocaine administered intravenously.

Atrial pacing studies by Rosen and co-workers[7] in patients with normal A-V conduction showed little or no effect of lidocaine on A-V nodal or intraventricular conduction. Josephson and co-workers[19] measured refractory periods before and after lidocaine in 14 patients (13 with normal conduction and one with RBBB and first degree A-V block). No consistent effect was found on the refractory periods of the atrium and A-V node, while lidocaine shortened the ERP and RRP of the His-Purkinje system.

Bekheit, Murtagh, and Fletcher[9] studied conduction intervals before and after lidocaine in 10 patients, four of whom had a prolonged HV interval. They found no significant effect on specialized conducting tissues even in the patients with impaired conduction. Gupta, Lichstein, and Chadda[20] published a study of 21 patients with intraventricular conduction disturbances who received lidocaine intravenously. In two patients lidocaine caused total heart block distal to the His bundle and in a third patient atrial pacing produced a Mobitz Type II block after lidocaine. One patient developed cardiac arrest after lidocaine. She died after unsuccessful resuscitation.

Recently, Kunkel, Rowland, and Scheinman[21] reported a study in 10 patients with intraventricular conduction defects who received 6 mg. of lidocaine per kilogram in 22 minutes. Peak levels ranged from 3 3 to 11 0 μg per milliliter and no significant changes of intraventricular or A-V nodal conduction were demonstrated.

It is clear that the results of these studies on the effects of lidocaine on conduction defects are contradictory. Our study is unique in that we assessed in a large number of patients with serious conduction and impulse formation disturbances the effect of lidocaine both during intravenous bolus injection and afterward at therapeutic plasma levels, verified by plasma levels, and that the conduction system was thoroughly tested by measurement of conduction

Table II Refractory periods of the atrium A V node and His Purkinje system before and after lidocaine at therapeutic plasma levels

	Type of conduction disturbance	ERP		FRP		FRP		ERP_{HP}	
		Before	After	Before	After	Before	After	Before	After
Group I									
7 Ja	RBBB LAH	–	–	480	460	605	580	–	–
8 Mo	Intermittent RBBB	320	–	–	–	465	–	530	555
9 Fe	RBBB Mobitz Type II	–	–	330	330	470	480	610	610
10 Ko	Mobitz Type II	260	250	–	–	<375	<390	390	405
11 Am	RBBB LAH	230	230	–	–	<365	<370	–	–
12 Kr	RBBB LAH	225	240	–	–	295	310	–	–
13 Me	RBBB LAH 2 1 Mobitz Type II	230	240	250	–	315	315	>560	>560
14 Ny	2 1 3 1 Mobitz Type II Total heart block	230	250	–	–	<350	<360	>6[illegible]0	>6[illegible]0
15 Ma	LBBB	–	–	280	230	460	350	–	–
Group II									
21 Bo	Wenckebach	<210	<230	–	–	670	670	–	–
22 Wa	Wenckebach	340	315	–	–	760	840	–	–
Group III									
29 Gm	RBBB LAH First degree A V block	300	340	545	530	665	645	–	–
Group IV									
36 Vl	Atrial quiescence Sinus arrest	330	330	440	470	600	590	–	–
37 Ga	Sinus arrhythmia LBBB	230	220	<230	315	<365	385	–	–
39 Di	Sinus arrest	305	310	–	–	<375	360	–	–

FRP = effective refractory period of the atrium
ERP = effective refractory period of the A V node
FRP = functional refractory period of the A V node
FRP = effective refractory period of the His Purkinje system
RRP = relative refractory period of the His Purkinje system

that lidocaine has no consistent effect on A V nodal conduction time during atrial pacing even in patients with high degree A V nodal block Considering the Wenckebach point again a lack of any consistent effect is clear In Fig 9 the WP during the control period is plotted on the abscissa and the WP after lidocaine on the ordinate The regression line

$$y = 0\,9x + 5\,7 \quad r = 0\,95$$

does not differ significantly statistically from y = x In Table II, the refractory periods of the A V node are tabulated

In three patients, the ERP shortened slightly after lidocaine in one patient, no change occurred, and in two patients the ERP became slightly prolonged The FRP of the A V node shortened in four patients remained constant in two and was prolonged in five The lack of a constant effect of lidocaine on pooled AH times Wenckebach point, and A V nodal refractory periods makes it unlikely that this drug has any effect at all on A V nodal conduction

Sinus node function at therapeutic plasma lidocaine levels In Table III, the sino atrial *recovery times before and after lidocaine* are listed together with the atrial effective refractory periods The SART *decreased in eight* of 12 patients without sinus node malfunction (in two patients statistically significant) and increased in four (with statistical significance in one) For all patients of Groups I II, and III together the mean SART before lidocaine was 954 3 ± 196 2 and after lidocaine 960 7 ± 183 7 This difference is statistically insignificant In patients with sinus node malfunction lidocaine prolonged the SART slightly but without statistical or clinical significance Atrial refractory periods were shortened by lidocaine in three patients with normal sinus node function (mean 15 msec), increased in three other patients (mean 22 msec) and were unchanged in one

In patients with sinus node malfunction the atrial refractory periods were hardly changed by lidocaine The PA intervals did not change during

RRP		Cycle length (msec)	Plasma lidocaine
Before	*After*		
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–	–	750	2 [illegible]
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These results differ from those of Bekheit Murtagh and Fletcher[19] which is probably explained by the small number of patients with intraventricular conduction disturbances studied by these authors They also differ from those of Kunkel Rowland and Scheinman[2] who found no influence of lidocaine on intraventricular conduction in 10 patients during or after infusion of 6 mg per kilogram in 22 minutes This difference is explained by their method of infusion which produced clearly toxic levels in only two patients Our method of administration is more comparable to common coronary care practice where mostly a shot of lidocaine is given followed by a drip infusion Moreover these authors did not perform atrial pacing and did not measure refractory periods so that possible effects of lidocaine may have been obscured

The results agree with those of Gupta Lichstein and Chadda who also found serious intraventricular conduction delay in 21 patients with pre existent lesions after intravenous lidocaine injection Considering the refractory periods of the His Purkinje system in the five patients in whom these could be measured it appears that these never shortened after lidocaine and increased in two patients These results are at variance with those of Josephson and co workers[8] in patients with normal intraventricular conduction in whom a consistent shortening was found after lidocaine Bigger and Mandel have shown that lidocaine in therapeutic concentrations increases conduction velocity in Purkinje tissue and the junction of Purkinje fibers and ventricular muscle whereas toxic concentrations slow conduction velocity Our observation that even therapeutic levels of lidocaine may impair infra His conduction in patients with pre existent lesions apparently means that these patients are more sensitive to a toxic effect of the drug An explanation of this difference between normal and diseased His Purkinje systems can only be speculative Possibly facilitation of conduction in normal parts of the His Purkinje system by lidocaine increases refractory periods and conduction velocity in diseased parts thereby increasing inhomogeneous conduction Unfortunately the technique of His bundle recording compels us to consider the His Purkinje system as a whole and makes measuring of the refractory periods of the different branching portions impossible

Our results concerning the effect of lidocaine on A V nodal conduction confirm earlier reports by Rosen and co workers[17] and Josephson and co workers[18] but extend these by the observation that even the highest degrees of A V nodal block are not influenced by lidocaine neither at therapeutic nor at toxic plasma levels

We found inconsistent changes of pooled AH times Wenckebach point and A V nodal refractoriness As do Bekheit Murtagh and Fletcher[19] we feel these changes should be ascribed to spontaneous variations in autonomous nervous control rather than to a direct drug effect The effect of lidocaine on the sinus node was evaluated in 19 patients with normal sino atrial function by means of SART Differences in both directions were small and mostly statistically insignificant Because in the literature patients have been described with sino-atrial arrest or marked sinus bradycardia[9,13,15] we included a group of nine patients in our study all satisfying the criteria for the sick sinus syndrome except patient No 38 who suffered from carotid sinus hypersensitivity As did Narula Samet, and Javier[25] we found both patients with almost normal and patients with extremely prolonged SARTS in this group In contrast to the patients with normal sinus node function the SART never decreased but increased slightly in all nine patients however without statistical or clinical significance Spontaneous sinus rate or the number of A V junctional escape beats did not change after lidocaine and the changes in atrial refractoriness were inconsistent

Like the A V node the sinus node is under autonomous nervous control which makes it likely that the observed and inconsistent changes are due to variations in vagal tone and not to an effect of the drug

Finally in three patients with complete block (one distal and two proximal to the His bundle) no effect was seen on the spontaneous firing rate of the escape focus The same result was found in two other patients with complete heart block distal to the His bundle who were not included in this study because no His bundle recordings were obtained

The results of our study have clinical implications Patients with conduction disturbances distal to the His bundle are prone to transient progressive deterioration of their conduction disturbance after intravenous bolus injection There is a clear relationship between the extreme plasma levels which this method of administration produces and the observed conduction

Table III Sino atrial recovery time and atrial refractoriness before and after lidocaine at therapeutic plasma levels

Patient No	SART before lidocaine (mean of 5 determinations ± SD in milliseconds)	SART after lidocaine (mean of 5 determinations ± SD in milliseconds)	Statistical significance	ERP (msec) before lidocaine	ERP (msec) after lidocaine	Cycle length (msec)
Groups I II III						
7	1 286 ± 116	1 106 ± 18	p < 0 02	–	–	–
8	1,226 ± 10 3	1 146 ± 144	ns	320	–	750
10	1 062 ± 30	1 043 ± 29	ns	260	250	00
11	958 ± 22	944 ± 23	ns	230	230	650
12	–	–	–	225	240	450
13	775	–	–	230	240	560
14	902 ± 156	958 ± 161	ns	230	250	620
15	850 ± 12	827 ± 12	ns	–	–	–
16	982 ± 25	960 ± 12	ns	–	–	–
21	697 ± 12	662 ± 27	ns	<210	<230	550
22	1 062 ± 29	977 ± 36	p < 0 02	340	315	860
27	852 ± 99	920 ± 142	ns	–	–	–
28	877 ± 83	1 010 ± 116	ns	–	–	–
29	980 ± 27	1 230 ± 49	p < 0 001	300	340	680
Group IV						
31	1 553	1 800	–	–	–	–
32	–	4 250	–	–	–	–
33	1 610	1 733	–	–	–	–
34	1 230 ± 41	1 370 ± 160	ns	–	–	–
35	9 180 ± 1 078	9 675 ± 3 179	ns	–	–	–
36	1 650 ± 246	1 762 ± 206	ns	330	330	800
37	980 ± 308	–	–	230	220	500
38	1 235 ± 26	1 290 ± 41	ns	–	–	–
39	1 002 ± 19	1 012 ± 50	ns	305	310	700

SART sino atrial recovery time
ERP effective refractory period of the atrium
In this patient complete sinus arrest followed atrial pacing Instead of the SART the A V nodal escape time is given in this case

intervals during sinus rhythm and atrial pacing and by comparison of the refractory periods We found that in seven out of 26 patients with impaired conduction in or below the His bundle intravenous bolus injection of 100 mg of lidocaine produced marked deterioration of intraventricular conduction This adverse effect coincided with peak plasma levels which reach extreme levels (mean 26 6 μg per milliliter) 60 seconds after the beginning of the injection and disappeared with the return of the plasma drug level to the therapeutic range

In patients with normal infra His conduction, no adverse effects were seen on A V nodal or intraventricular conduction even at the highest plasma levels and even in patients with high degrees of A V nodal block

Therapeutic plasma lidocaine levels influenced His Purkinje conduction in only one patient during sinus rhythm In this patient who had incomplete RBBB in the control period an increasing number of beats had complete RBBB with increasing plasma lidocaine levels Because of the close relationship between plasma levels and right bundle branch conduction a mechanical cause of the decremental conduction by the His bundle electrode is unlikely (Fig 5)

Stressing of the conduction system by atrial pacing at therapeutic levels however again produced deterioration of infra His conduction in five patients with pre existent lesions an increase of second degree block distal to the His bundle in three patients and an increase in the number of beats with complete bundle branch block in two patients with incomplete or intermittent bundle branch block Mechanical conduction impairment by the His bundle electrode wire is excluded by the very fact that these conduction defects were induced by atrial pacing and thus are frequency dependent

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defects Intravenous bolus injection of lidocaine is clearly a hazard in patients with distal conduction defects However even at therapeutic plasma levels some of these patients show decreased intraventricular conduction during stress by atrial pacing or an increase of His Purkinje refractoriness To translate these electrophysiological effects into terms of clinical risk is difficult The risk of therapeutic plasma lidocaine levels in patients with distal conduction defects might however, turn out to be small since in this study none of the patients developed symptoms and only one patient showed decreased bundle branch conduction during sinus rhythm without consequence for 1 1 A V conduction Until more is known it seems wise to give lidocaine to such patients under continuous ECG monitoring and with immediate availability of pacemaker facilities To avoid peak plasma levels the drug should be given by intramuscular or slow intravenous injection

On the other hand lidocaine has not been shown to be detrimental to A V nodal conduction or sinus node function, even in patients with severe defects and at the highest plasma levels Therefore the drug seems harmless in these patients and should not be withheld if its use may be to their benefit

Summary

The acute electrophysiologic effects of a bolus injection of 100 mg of lidocaine were investigated in 39 patients with impulse formation and conduction defects by means of His bundle recording and were correlated with plasma lidocaine levels

The effects of therapeutic plasma levels on conduction intervals and refractory periods were subsequently studied during sinus rhythm and atrial pacing The sinus node function was studied by measurement of the sino atrial recovery time

Seventeen patients had conduction defects in or distal to the His bundle, six exclusively proximal to the His bundle and nine at both levels Nine patients had pre existent sinus node malfunction Ten out of 39 patients suffered from acute myocardial infarction Two patients were studied twice because of changed A V conduction

Intravenous injection of 100 mg of lidocaine within 20 seconds produced peak arterial plasma levels (mean 26 6 μg per milliliter) 60 seconds after the beginning of the injection

Seven out of 26 patients showed transient progression of their pre existent infra His conduction impairment, coincident with peak plasma levels apparently due to drug toxicity Even at therapeutic plasma levels, five out of 26 patients showed decremental intraventricular conduction during atrial pacing when compared to control tracings His Purkinje refractoriness was not shortened in these patients and increased in two Lidocaine had no effect on ventricular automaticity in three patients with complete heart block Lidocaine had no consistent effects on sinus rate SART atrial refractoriness or A V nodal conduction as measured by pooled AH intervals and the Wenckebach point, and on A V nodal refractoriness

It is concluded that lidocaine is safe in patients with high degrees of A V nodal block and in patients with impulse formation disturbances However patients with intraventricular conduction defects are prone to deterioration of their conduction disturbance due to drug toxicity

The drug should be given to such patients preferably if monitoring and pacemaker facilities are available and by the intramuscular route to avoid peak plasma levels

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Table I Patients clinical characteristics*

Patient	*Age*	*Sex*	*ECG*	*Prior cardiac medications (daily dosage)*	*PVC coupling interval† (sec)*	*Parasystole‡*	*Major medical diagnoses*
1	38	M	Minor non specific T wave abnormalities Voltage criteria for slight LVH	Propranolol 80 mg (–) Quinidine dosage unknown (–) Procaine amide 2 000 mg (–)	0 0-0 6	Probably not	Labile hypertension H/O pyelonephritis
	[illegible]	F	Minor non specific T wave abnormalities	None	0 47 0 60	Probably not	H/O possible pulmonary embolus in past
3	34	F	WNL	None	0 38	No	None
4	31	F	–30 QRS axis	Quinidine 600 mg (+)	0 7? 0 86	Probably not	None
5	31	F	WNL	Procaine amide 1 000 mg (–)	0 43-0 59	Probably not	None
6	[illegible]	M	WNL	None	0 69	No	None
	21	M	WNL	None	0 48-0 66	Probably not	None
8	22	F	WNL	None	0 47	No	None
9	25	F	WNL	None	0 48	Too few PVC s to determine	H/O possible pulmonary emboli in past
10	3	M	Possible RVH	None	0 4 0 59	Probably not	None
11	25	F	WNL	None	0 4 -0 61	Probably not	None
12	39	F	WNL	Procaine amide 1 000 mg (–) Propranolol 40 mg (–)	0 5?	No	Diabetes mellitus Labile hypertension

Abb e iat ns H/O hi t ry f LVH RVH l ft right ntricular hypert ophy WNL w thin ormal lim ts (–) PVC s not suppressed (+) PVC s suppressed

†PVC oupling int rv l wa d termined e ther f m the pat nt control ECG f r this study or from a re ent resting ECG

‡Para ystole was judged p bably not p esent when th PVC coupl g nt rval aried b t no fixed parasystolic interval ould be f und

ry physical examination resting and exercise (generally the standard double Master s test) electrocardiograms and either a four view cardiac x ray series with barium swallow or a cardiac fluoroscopy A battery of chemical and hematologic blood tudies as well as a urinalysis was carried out on the day of the study Patient No 1 showed borderline cardiac enlargement on chest x ray with a cardiothoracic ratio of 16/33 Patient No 12 who was diabetic had hyperglycemia Electrocardiogram findings which were minor are listed in Table I Otherwise these screening tests showed no significant abnormalities

Procedure of study Patients took no drugs known to affect the cardiovascular system for at least three days prior to study they were not taking any drugs whose effect might persist for longer than this period of abstinence (except for patient No 12 who took insulin) Patients were studied in the fasting state The electrocardiogram (Lead II) was monitored continuously Blood pressure (BP) was measured intermittently by indirect methods (arm cuff)

Patients lay supine in bed throughout the study All drugs were given intravenously through an indwelling plastic catheter with a slow continuous 0 9 per cent saline flow After a control period of five minutes a placebo dose of 2 0 c c of 0 9 per cent saline was administered After five minutes or a return to the control levels of HR and BP the first active pharmacologic agent was given The drugs generally were administered in the order listed below The effects of the prior drug had abated (as judged by HR and BP) before the next agent was given this time period varied from three minutes (edrophonium 1 mg) to two hours (atropine) PVC incidence (i e PVC per minute) generally returned to control levels also The drugs administered were

Vagally mediated suppression of premature ventricular contractions in man

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Prior studies have demonstrated the importance of the autonomic nervous system in the genesis and suppression of premature ventricular contractions (PVC's). Sympathetic nerve activity[1-4] and imbalance[5] have been shown to increase ventricular irritability. Afferent vagal nerve stimulation also has been shown to increase PVC frequency.[6] In addition, there is evidence that vagal activity can decrease ventricular irritability in certain situations.[7-9]

Kent and associates[7] showed that vagal stimulation increased the threshold for electrically induced ventricular fibrillation in dogs with experimentally produced myocardial ischemia. This effect was separable from the bradycardia produced by the vagal stimulation. Corr and Gillis showed that the vagus nerves protected dogs against fatal ventricular arrhythmias following experimental coronary artery occlusion. Vagotomy or pretreatment with atropine increased significantly the occurrence of arrhythmic death in those groups as compared with control subjects, while atrial pacing to the same heart rate produced by vagotomy and atropine did not. The authors concluded that efferent vagal tone per se was responsible for reducing the number of deaths. Weiss and Engel[9] studied the ability of patients to control PVC's voluntarily. In one of their patients who was able to inhibit the occurrence of PVC's for long periods in association with bradycardia, pharmacologic studies suggested that increased vagal tone to the heart was the mediating mechanism, i.e., phenylephrine or edrophonium each suppressed PVC's.

The purpose of this study was to explore further the possible role of the vagus nerves in suppressing PVC's in man. This was done by administering a series of autonomically active drugs to patients with PVC's, including agents which stimulated (phenylephrine, edrophonium) and blocked (atropine) the vagus nerves to the heart. As these vagotonic and vagolytic agents commonly produce large heart rate (HR) changes, we attempted to control for these effects. Propranolol, the beta sympathetic blocker, was administered as another means of decreasing HR, and isoproterenol, the beta sympathetic agonist, was given as another means of increasing HR. Atrial pacing was not employed to increase HR, as the benign character of the PVC's in these patients appeared to contraindicate cardiac catheterization.

Materials and methods

Patient selection and prestudy evaluation. Twelve patients with PVC's were studied in the Clinical Research Center of the Hospital of the University of Pennsylvania. All patients were under forty and without evidence of significant heart disease. (All were classified IA by the New York Heart Association Functional and Therapeutic Classifications.) The patients' clinical characteristics are detailed in Table I.

The patients were evaluated by medical histo

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Table II Drug effects in five patients with vagally suppressible PVC s

Drug		$\overline{HR}$ (bpm)	$\overline{PVC}$ (per minute)	$\overline{\% PVC}$
Control		63 2 (54 8- 78 0)	11 0 (4 4 16 3)	18 1 (0)
Placebo		63 2 (54 8- 79 6)	10.8 (5 ? 18 0)	18 2
Phenylephrine		48 5 (39 8 54 0)	1 5 (0 5- 4 0)	3 2 (5)
Edrophonium		62 5 (46 7 76 5)	9 7 (1 7 24 8)	15 0 (1)
Atropine		102 8 (87 5- 115 0)	10 , (0 26 5)	11 1 (3)
Isoproterenol	(n = 4)	101 7 (87 2 116 4)	11 5 (0 31.5)	10 5 (?)
	(n = 5)	97 5 (80 7 116 4)		
Propranolol	(n = 3)	67 5 (55 8 79 7)	17 6 (6 7 30 0)	27 1 (0)
	(n = 5)	79 3 (55 8- 97)		
Isoproterenol after propranolol	(n = 3)	67 8 (53 0- 78 0)	19 2 (7 5-33 2)	29 5 (0)
	(n = 5)	71 7 (59 0- 8? 9)		

Numbers in table for $\overline{HR}$ $\overline{PVC}$ and $\overline{\% PVC}$ are mean values for the five patients. Where data were eliminated because PVC incidence had not returned to the control level before that drug was administered, this is shown by an n = 3 or n = 4 row average heart rate in these situations is also shown for all five patients in the n = 5 row Numbers in parentheses for $\overline{HR}$ and $\overline{PVC}$ columns show the range of individual patient s mean values Numbers in parentheses for $\overline{\% PVC}$ column indicate the number of patients showing statistically significant decreases in % PVC ($p < 0.0?5$ at least) by chi square frequency analysis versus the placebo effect
$\overline{\% PVC} = \overline{PVC}/\overline{HR} \times 100$

Table III Drug effects in patients No 1 and 2

Dru₀	*Patient No 1*			*Patient No 2*		
	$\overline{HR}$ (bpm)	$\overline{PVC}$ (per minute)	% PVC	$\overline{HR}$ (bpm)	$\overline{PVC}$ (per minute)	% PVC
Control	56 8 (0 8)	13 8 (0 8)	24 3	67 7 (0 b)	16 3 (? 0)	24 1
Placebo	55 8 (0 4)	14 0 (1 6)	25 1	66 5 (0 5)	11 2 (2 3)	16 8
Phenylephrine (40 μg/min)	46 8 (6 5)	4 0 (2 6)	8 5	54 0 (1 6)	0 6 (1.3)	1 1
Edrophonium (10 mg)	46 7 (0 4)	1 7 (1 7)	3 6	76 5 (1 1)	12.5 (3 6)	16 3
Atropine (1.5 mg	87 5 (1 1)	26 5 (1 6)	30 3	101 2 (1 1)	?1.5 (7 7)	21 2
?0 mg [total])	90 0 (1 2)	8 2 (1 8)	31 3			
Isoproterenol						
(1 5 μg/min)	87 2 (2 9)	8 0 (0 7)	9.2			
(? 0 μg/min)	96 6 (4 3)	2 4 (? 2)	2 5	93 6 (1 0)	0 (0)	0
Propranolol (3 mg)	55 8 (1 5)	13 (1 9)	23 6		Data eliminated†	
Isoproterenol after propranolol (2 0 μg/min)	59 0 (1 6)	17 0 (0 8)	28 8		Data eliminated†	

Numbers in table for $\overline{HR}$ and $\overline{PVC}$ are mean values. Standard deviations are in parentheses
($p < 0.001$) by chi-square frequency analysis versus the placebo effect
†Data were eliminated when PVC incidence had not returned to the control level before the next drug was administered.
% PVC = $\overline{PVC}/\overline{HR} \times 100$

tion data for the next drug were eliminated This procedure removed one source of false positive results

Results

Two of the twelve patients studied were not having PVC s at the time of drug testing Of the remaining ten patients five (patients Nos 1 2 4 8 and 11) showed a significant decrease in the percentage of ventricular heart beats which were PVC s (per cent PVC) during phenylephrine administration (Table II Fig 1) Among these five patients the mean per cent PVC was 18 2 per cent following placebo During phenylephrine administration it fell to 3 2 per cent ($p<0.005$ in each case) The average PVC incidence also decreased from 10 8 per minute to 1.5 per minute A large decrease in HR also occurred in each patient during phenylephrine administration The mean HR was 63 2 beats per minute (bpm) following placebo and 48 5 bpm during phenylephrine administration

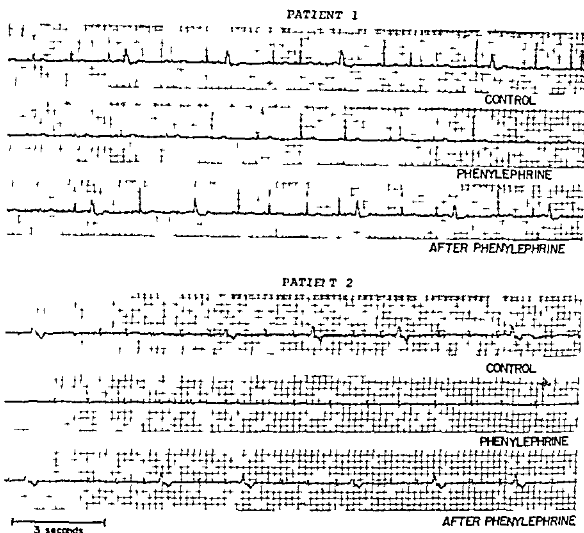


Fig 1 Electrocardiogram rhythm strips (Lead II) from two patients (patients Nos 1 and 2) showing typical rhythm responses to drug interventions among the five patients in the vagally suppressible PVC group PVC s were suppressed by phenylephrine they returned after the phenylephrine was stopped

phenylephrine (10 to 60 μg per minute for three to six minutes at each dosage)[10] edrophonium (1 to 10 mg)[11] atropine (1 5 to 2 mg),[12] isoproterenol (0 5 to 2 0 μg per minute for three to six minutes at each dosage)[13] and propranolol (3 mg)[14] Isoproterenol was re administered about five minutes following propranolol to test the effec tiveness of the blockade

Data processing and analysis Heart rate and PVC incidence were determined by manual counts from the electrocardiogram record when the drug s effect was maximal and stable Three to five minutes of continuous electrocardiogram monitoring was counted for each drug Mean HR per minute ($\overline{HR}$) and mean PVC incidence per minute ($\overline{PVC}$) were calculated from these data Standard deviations for HR and PVC incidence were calculated from the variance among one minute epochs in the sample The per cent of ventricular heart beats which were PVC s also was calculated (per cent PVC = $\overline{PVC}/\overline{HR}$ × 100)

Statistical tests of significance were carried out using a chi square frequency analysis samples of equal duration were compared The statistical comparisons were made between the patient s response to placebo and to a given drug In this regard one problem arose from spontaneous fluc tuations in the patient s PVC level which some times occurred during the 4 to 6 hour study We dealt with this by recording several minutes of electrocardiogram monitoring prior to adminis tering each drug When subsequent data analysis showed that a statistically significant change in per cent PVC had occurred spontaneously be tween the administration of two drugs or that the per cent PVC had not returned to the control level following the previous drug s administra

are consistent with anatomic evidence of vagal innervation of the mammalian ventricle[1,1] as well as with physiologic studies showing vagally mediated effects on ventricular performance[19,1]

We do not wish to assert that the vagus nerves are the only means of suppressing PVCs in these patients The fact that atropine also suppressed PVCs in three of the five patients underscores this However strongly increased vagal tone appears to be one means of suppressing PVCs in a significant number of patients

The attempt to control for the bradycardia associated with phenylephrine by subsequently administering propranolol was unsuccessful Propranolol in the intravenous dosage we employed did not lead to HR decreases However the animal studies by Kent and co workers and Corr and Gillis mentioned earlier did control adequately for HR changes There they did not appear to be the mediating mechanism

Several possibilities exist to account for the observation here of vagally suppressible PVCs (1) The decreased PVC incidence and per cent PVC may have been secondary to the associated bradycardia e g with its concomitant decrease in myocardial energy demands However as noted above animal studies suggest this is not the *major factor* (2) If the PVCs originate in an ectopic focus the vagus may directly decrease its rate of firing Spear and Moore have shown that brief vagal nerve stimulation can slow idioventricular pacemakers in the dog Furthermore Benforado has shown that vagal stimulation inhibits the establishment of idioventricular pacemakers in isolated perfused rat hearts An *ectopic* focus also may be slowed by vagally released acetylcholine (ACh) Thus Benforado showed that ACh decreases the frequency *of contraction* of rabbit ventricles in vitro (3) A third explanation might be that vagal discharge inhibits PVCs occurring by a re entry mechanism This might occur in at least two ways (a) vagal activity may alter conduction velocity In this regard Bailey and associates have demonstrated that ACh applied in vitro to the His Purkinje specialized conduction system of the dog increases conduction velocity Thus the vagus might suppress reentrant PVCs by opposing decremental conduction in ventricular conduction tissue (b) The vagus may alter ventricular repolarization Greenspan Wunsch and Fisch showed that stimulation of the distal end of the crushed vagus nerve in dogs led to marked changes in T wave configurations This was true in both the normokalemic and hyperkalemic states Although both patients Nos 1 and 2 in the present study had T wave abnormalities we could not evaluate the possible amelioration of this when PVCs were suppressed pharmacologically because only Lead II was recorded during the study (4) At the biochemical level ACh acts primarily through the cyclic guanosine monophosphate (cGMP) system[6] Thus increased vagal tone may change PVC frequency by affecting cGMP metabolism in patients with vagally suppressible PVCs

The additional observation here that atropine produced a higher PVC incidence in two of the patients may be relevant to previous clinical reports Aministration of methyl scopolamine[7] or atropine has been observed at times to lead to increased ventricular irritability in patients with recent myocardial infarction or other severe heart disease Massumi and co workers[28] hypothesized that this might be related to the atropine induced tachycardia with concomitant increase in myocardial oxygen demand This study suggests the additional possibility that atropine may enhance PVC incidence specifically by its vagal blocking effect rather than by means of tachycardia This is consistent with the findings of Kent and associates and Corr and Gillis that vagal stimulation protected dogs against *ventricular arrhythmias* while vagotomy or *pretreatment with atropine* increased the occurrence of arrhythmias and arrhythmic death

Lown and associates observed a significant decrease in PVC incidence in patients during sleep They hypothesized that this might be secondary to decreased cardiac sympathetic nerve activity The bradycardia occurring during sleep has been shown to be mediated in large measure by the vagus nerves in cats[30] and in man slowing of cardiac rate has been shown to be primarily due to parasympathetic neural control[1] Thus the decrease in PVCs which Lown and co workers observed may be related in part to increased vagal tone a hypothesis consistent with this study s findings

Because of the observed association between PVCs and sudden cardiac death (generally in older patients than these[13,1]) this study may have therapeutic relevance Our findings suggest that in certain patients with PVCs maneuvers to increase vagal tone to the heart strongly may

Edrophonium produced smaller decreases in HR and less consistent decreases in per cent PVC in these five patients In only one of them (patient No 1) was the decrease in per cent PVC statistically significant

Propranolol was given in an effort to control for the HR decreases produced by the vagotonic agents In two of the five patients (patients Nos 2 and 4) the propranolol data were eliminated because of a spontaneous change in PVC incidence before the drug was administered Propranolol did not produce a significant decrease in per cent PVC in any of the remaining three patients nor did it decrease average HR Thus it was not an adequate control for the phenylephrine induced bradycardia (However this also underscores the fact that strong vagal stimulation can reduce HR to a greater extent than acute intravenous beta sympathetic blockade)

Among the five patients who decreased PVC s in response to phenylephrine two (patients Nos 1 and 2) also showed the converse namely an increase in PVC incidence following atropine administration In patient No 1 PVC s increased from 14 0 per minute to 26 5 per minute in patient No 2 from 11 2 per minute to 21 5 per minute However because of the concomitant atropine induced tachycardia the per cent PVC did not show a statistically significant change The complete data from these patients are shown in Table III In the other three patients atropine led to a significant decrease in per cent PVC

Isoproterenol used as a control for the atropine induced tachycardia decreased the per cent PVC in two of the five patients (Nos 1 and 2) Here also one of the five patients data (patient No 8) was eliminated because of a spontaneous change in PVC incidence preceding isoproterenol administration

In only one of the twelve patients studied did phenylephrine produce a minor but statistically significant increase in PVC s In patient No 9 it led to an increase in the per cent PVC—from 0 to 3 4 per cent ($p<0\ 025$)—while PVC incidence increased from 0 to 1 5 per minute

No feature distinguished the five patients who showed PVC suppression with phenylephrine from the five patients who did not Resting HR level, clinical history and site of origin of the PVC s did not differ in any apparent pattern between the two groups (Ten of the twelve patients PVC s were right ventricular in origin, patient No 11's PVC s were left ventricular in origin, and patient No 10 s PVC s were not recorded in enough different electrocardiogram leads to determine their site of origin)

Discussion

A number of studies have shown that autonomic nervous system activity can affect the incidence of premature ventricular contractions Several studies have demonstrated the capacity of the cardiac sympathetic nerves to increase PVC s Thus Gillis[1] showed that increased ventricular irritability associated with experimental digitalis intoxication in cats was accompanied by an increased number of cardiac sympathetic nerve impulses Furthermore he and his associates showed that the threshold for such digitalis induced ventricular fibrillation could be increased by pharmacologic agents which diminished the number of these impulses [1 3] Estes and Izlar[4] treated a patient having recurrent episodes of ventricular tachycardia with bilateral cardiac sympathectomy This patient s ventricular irritability was controlled thereafter Yanowitz Preston and Abildskov[11] demonstrated that an imbalance between the neural activity of the right and left stellate ganglia could produce localized changes in myocardial functional refractory period in dogs Such changes have been shown to increase ventricular irritability [1] Moss and McDonald[5] treated a patient who had a prolonged Q T interval and recurrent episodes of ventricular fibrillation, with unilateral sympathetic ganglionectomy After this treatment the patient had no further episodes of fibrillation

Other reports also emphasize the importance of the vagus nerves in PVC s Scherf Blumenfeld and Yildiz[6] studied dogs which had PVC s produced experimentally by application of aconitine directly to the heart They found that when the PVC s produced by this procedure had stopped stimulation of the central end of the cut vagus nerve caused them to recur In addition, several studies [9] indicate that increased vagal activity can decrease ventricular irritability

The data presented here also suggest that some patients have vagally suppressible PVC s Five of the ten patients (50 per cent) having PVC s at the time of study showed a statistically significant decrease in per cent PVC with strong phenylephrine induced increases in vagal tone These findings of vagal influence on ventricular irritability

are consistent with anatomic evidence of vagal innervation of the mammalian ventricle[17,18] as well as with physiologic studies showing vagally mediated effects on ventricular performance[19-21]

We do not wish to assert that the vagus nerves are the only means of suppressing PVCs in these patients The fact that atropine also suppressed PVCs in three of the five patients underscores this However strongly increased vagal tone appears to be one means of suppressing PVCs in a significant number of patients

The attempt to control for the bradycardia associated with phenylephrine by subsequently administering propranolol was unsuccessful Propranolol in the intravenous dosage we employed did not lead to HR decreases However the animal studies by Kent and co workers and Corr and Gillis[8] mentioned earlier did control adequately for HR changes There they did not appear to be the mediating mechanism

Several possibilities exist to account for the observation here of vagally suppressible PVCs (1) The decreased PVC incidence and per cent PVC may have been secondary to the associated bradycardia e g with its concomitant decrease in myocardial energy demands However as noted above animal studies[8] suggest this is not the major factor (2) If the PVCs originate in an ectopic focus the vagus may directly decrease its rate of firing Spear and Moore have shown that brief vagal nerve stimulation can slow idioventricular pacemakers in the dog Furthermore Benforado has shown that vagal stimulation inhibits the establishment of idioventricular pacemakers in isolated perfused rat hearts An ectopic focus also may be slowed by vagally released acetylcholine (ACh) Thus Benforado showed that ACh decreases the frequency of contraction of rabbit ventricles in vitro (3) A third explanation might be that vagal discharge inhibits PVCs occurring by a re entry mechanism This might occur in at least two ways (a) vagal activity may alter conduction velocity In this regard Bailey and associates have demonstrated that ACh applied in vitro to the His Purkinje specialized conduction system of the dog increases conduction velocity Thus the vagus might suppress re entrant PVCs by opposing decremental conduction in ventricular conduction tissue (b) The vagus may alter ventricular repolarization Greenspan Wunsch and Fisch showed that stimulation of the distal end of the crushed vagus nerve in dogs led to marked changes in T wave configurations This was true in both the normokalemic and hyperkalemic states Although both patients Nos 1 and 2 in the present study had T wave abnormalities we could not evaluate the possible amelioration of this when PVCs were suppressed pharmacologically because only Lead II was recorded during the study (4) At the biochemical level ACh acts primarily through the cyclic guanosine monophosphate (cGMP) system Thus increased vagal tone may change PVC frequency by affecting cGMP metabolism in patients with vagally suppressible PVCs

The additional observation here that atropine produced a higher PVC incidence in two of the patients may be relevant to previous clinical reports Administration of methyl scopolamine[27] or atropine[8] has been observed at times to lead to increased ventricular irritability in patients with recent myocardial infarction or other severe heart disease Massumi and co workers[28] hypothesized that this might be related to the atropine induced tachycardia with concomitant increase in myocardial oxygen demand This study suggests the additional possibility that atropine may enhance PVC incidence specifically by its vagal blocking effect rather than by means of tachycardia This is consistent with the findings of Kent and associates[7] and Corr and Gillis that vagal stimulation protected dogs against ventricular arrhythmias while vagotomy or pretreatment with atropine increased the occurrence of arrhythmias and arrhythmic death

Lown and associates observed a significant decrease in PVC incidence in patients during sleep They hypothesized that this might be secondary to decreased cardiac sympathetic nerve activity The bradycardia occurring during sleep has been shown to be mediated in large measure by the vagus nerves in cats and in man slowing of cardiac rate has been shown to be primarily due to parasympathetic neural control[31,32] Thus the decrease in PVCs which Lown and co workers observed may be related in part to increased vagal tone a hypothesis consistent with this study's findings

Because of the observed association between PVCs and sudden cardiac death (generally in older patients than these[1,2]) this study may have therapeutic relevance Our findings suggest that in certain patients with PVCs maneuvers to increase vagal tone to the heart strongly may

decrease PVC incidence It would seem wise however, to exclude patients who already have severe bradycardia Our data indicate that major increases in vagal tone—here produced by phenylephrine—are required to suppress PVC s in the patients who do respond Edrophonium did not produce bradycardia or PVC suppression consistently in the doses employed here

Gillis and associates[1-3] have shown that drugs which diminish the frequency of cardiac sympathetic nerve firing decrease the incidence of ventricular arrhythmias produced by digitalis intoxication in animals In a parallel fashion patients with vagally suppressible PVC s may be benefited by drugs which strongly increase vagal nerve tone to the heart In the acute inpatient situation intravenous phenylephrine administration appears to be the method of choice For chronic, outpatient treatment it seems unlikely that orally administered drugs will produce sufficient cardiac vagotonia to be effective The use of carotid sinus nerve stimulation[16] might produce enough of an increase in vagal tone to be effective in the outpatient setting for patients refractory to other treatments

This study examined only relatively young and healthy patients Further work is needed to determine the validity of the findings for older patients with PVC s who have more serious heart disease The potential hazards of intravenous phenylephrine or carotid sinus nerve stimulation in treating PVC s in such patients also must be evaluated

Summary

Twelve patients with PVC s were studied to assess the possible role of the vagus nerves in suppressing PVC s All were without significant heart disease and under forty years of age A series of five autonomically active drugs including vagotonic and vagolytic agents was administered intravenously, each drug being given after the effects of the previous one had abated

Two of the patients did not have PVC s at the time of study Of the remaining ten patients five showed vagally mediated suppression of PVC s Phenylephrine (40 to 60 μg per minute) reduced HR, from an average of 63 2 bpm to 48 5 bpm by a vagally mediated reflex, and decreased PVC incidence in all five patients The per cent of ventricular heart beats which were PVC s (per cent PVC) decreased from an average of 18 2 per cent to 3 2 per cent in these patients ($p < 0\ 005$ in each case) Edrophonium (10 mg) produced less bradycardia and less reliable PVC suppression In two of these five patients atropine (1 5 mg) increased PVC incidence markedly, although the per cent PVC did not change significantly because of the concomitant tachycardia

These data suggest that strongly increased vagal tone can suppress PVC s in a significant percentage of such patients This finding in man extends previous animal work which has shown a protective role of the vagus against ventricular arrhythmias under certain conditions

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Myocardial perfusion imaging with ^{99m}Tc or ^{113m}In macroaggregated albumin Correlation of the perfusion image with clinical, angiographic, surgical, and histologic findings

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Precise definition of ischemic and scarred segments of left ventricular myocardium is of major clinical importance Revascularization of ischemic segments may relieve ischemia and improve myocardial performance, while enhanced delivery of blood to areas of the ventricular myocardium which are predominantly scar tissue will do neither This information regarding the state of the myocardium is not fully provided by current electrocardiographic (ECG), angiographic or hemodynamic techniques [1-3]

Myocardial perfusion imaging following the direct intracoronary injection of particulate radiopharmaceuticals allows external visualization of the relative distribution of coronary blood flow at the capillary level Since the state of the myocardium is directly related to blood supply in patients with atherosclerotic disease this technique potentially provides a method for assessing the presence of regional ischemia and scar due to infarction

This report compares the results of myocardial perfusion imaging with clinical history ECG left ventriculography, coronary angiography and surgical and autopsy findings in 77 patients Perfusion defects in the myocardial images will be shown to be related primarily to scar due to previous infarction or, in a few cases to regional ischemia in patients with the syndrome of preinfarction angina

Methods

A total of 77 myocardial perfusion images were performed in 76 supine resting patients undergoing diagnostic coronary arteriography Patients with congenital or valvular heart disease were excluded from this study The left coronary artery alone was imaged in 57 patients the right coronary artery alone in seven patients and both the left and right coronary arteries in 13 patients All were fully informed of the investigative nature of the study

All patients had a complete history physical examination and ECG ECG s were interpreted as positive for myocardial infarction only if typical Q waves of 0 04 second duration were present Additionally, the probability of past myocardial infarction was assessed as follows none—no clinical or ECG evidence of infarction possible—episodes of prolonged severe pain no ECG Q waves, probable—clinical history of infarction negative or equivocal ECG, or ECG Q waves alone and definite—ECG Q waves appropriate clinical history, and enzyme documentation

Coronary arteriography was performed using either the Sones or the Judkins technique Coronary arteriograms were interpreted by at least two observers The area of the most severe narrowing was measured and the severity of stenosis expressed as the per cent of diameter

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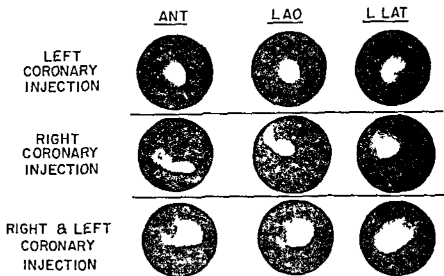


Fig 1 Injection of the left coronary artery (top row) produces an elliptical (ANT or L LAT) or spherical (LAO) pattern an inferior wedge of less activity is produced by perfusion of the inferior system from the right coronary artery Injection of the right coronary artery (middle row) produces a ball and tail configuration the former reflecting perfusion of the inferior left ventricle the latter perfusion of the right ventricle Injection of both arteries shows uniform perfusion of the left ventricle with a small right ventricular appendage Abbreviations *ANT* anterior *L LAT* left lateral and *LAO* left anterior oblique

narrowing as compared to the diameter of the most proximal normal area of vessel Biplane left ventriculography was performed using 0.75 to 1.0 cc per kilogram of radiographic contrast material filmed at 12 frames per second (roll films) or 60 frames per second (cine filming) Left ventricular volumes and systolic ejection fraction (SEF) were determined by the length area method of Dodge and co workers The ventricular contraction pattern was assessed in both planes and graded as normal (I) borderline abnormal (II) localized akinesis or hypokinesis (III) localized dyskinesis (IV) or diffuse hypo or akinesis (V) using the method of Hamilton Murray and Kennedy[5]

High specific activity ^{99m}Technetium or ^{113m}Indium macroaggregated albumin (TcMAA In MAA) was prepared using stannous chloride The MAA contained 1.5 to 3.0 mCi of ^{99m}Tc or ^{113m}In on 30 000 to 60 000 particles of MAA Ninety per cent of the particles were from 20 to 40 μ in size with no particles exceeding 100 μ in diameter Following coronary angiography the tagged MAA was injected directly into one or both coronaries flushed in with 5 c c of saline and the catheter position confirmed by angiography A delay of two minutes was observed between the last injection of radiographic contrast media and the injection of MAA to allow coronary flow to return to a near basal level[7] Following completion of the catheterization procedure patients were taken directly to the Nuclear Medicine Laboratory imaging was usually started within 30 minutes of the time of MAA injection and required 3 to 10 minutes per view One hundred thousand count Polaroid scintiphotos were obtained using a Nuclear Chicago HP gamma camera in the right anterior oblique anterior left anterior oblique left lateral left posterior oblique and posterior positions Camera collimation varied depending on whether ^{99m}Tc ^{113m}In or both had been injected in most cases a 4 000 parallel hole medium energy collimator was employed Two patients experienced transient angina at or near the time of MAA injection there were no ECG or intracoronary pressure changes during or immediately following injection

Myocardial perfusion images were read by two independent observers without knowledge of the clinical history or laboratory data The normal image was defined as uniform perfusion of the arterial bed injected—the abnormal image as a clearly discernible region of diminished activity Intra observer variation was minimal in two studies only one observer described regions of slightly decreased perfusion An additional three

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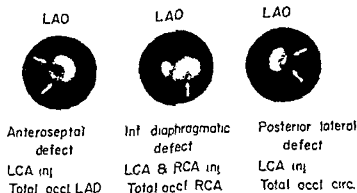


Fig 3 Typical image defects in the LAO view the left image showing decreased activity anteriorly the center image showing decreased activity inferiorly with hang up of activity in the proximal right coronary artery and the right image showing decreased activity posterolaterally These defects corresponded to anteroseptal inferior and lateral myocardial infarctions Abbreviations *occl* occluded *inf* inferior *inj* injection *LCA* left coronary artery and *RCA* right coronary artery

probable and 25 as definite Ninety six per cent of the patients (24/25) in the latter group had abnormal images while only one of those without infarction had an abnormal image (Fig 4) Electrocardiographic Q waves were present in 28 patients all but one of these had abnormal images However only 66 per cent of the group with abnormal images had Q waves

The mean systolic ejection fraction (SEF) for the group with normal images with 63 ± 11 per cent compared to 43 ± 15 percent ($p < 0.005$) for those with abnormal images Abnormal myocardial images were found in 38 per cent (17/45) of patients with normal or borderline abnormal contraction patterns (Grades I and II) In patients with definitely abnormal contraction patterns (Grades III IV and V) 92 per cent (23/25) had abnormal perfusion images (Fig 5)

The severity of stenosis of each major coronary artery and the interpretation of the myocardial perfusion images are shown in Table I Nineteen patients had normal coronary arteries or less than 50 per cent reduction in luminal diameter Myocardial perfusion images were normal in all of these patients Thirty three patients had complete occlusion of at least one coronary artery Twenty nine of these had corresponding image defects four did not None of the latter group had evidence of infarction by clinical, ECG or contraction pattern criteria

Two patients died within two months of imaging (one at the time of revascularization and the second following carotid artery surgery) Each was found to have had old transmural myocardial infarctions at autopsy which corresponded to

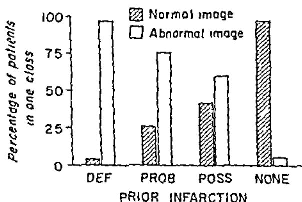


Fig 4 The percentage of patients with normal or abnormal images in one clinical subgroup Subgroups depict clinical history of myocardial infarction (as described in Methods) *Def* definite (25 patients) *Prob* probable (8 patients) *Poss* possible (17 patients) and *None* (22 patients) (Same footnote as in Methods)

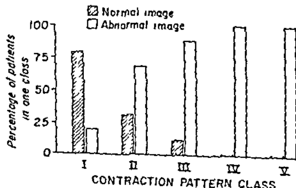


Fig 5 The percentage of patients with normal or abnormal images in one contraction pattern class (as described in methods) I = 29 patients II = 16 patients III = 17 patients IV = 5 patients and V = 3 patients (Same footnote as in Methods.)

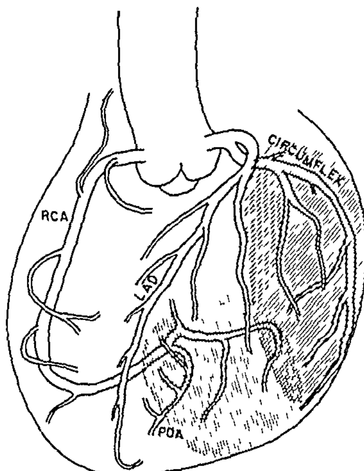


Fig 2 The anatomy of a dominant right coronary artery system (posterior descending artery arising from the right coronary) is overlaid with the three major perfusion image zones in the LAO view The left anterior descending coronary (LAD) artery supplies the anteroseptal portion of the sphere the circumflex coronary artery the posterolateral portion the posterior descending artery (PDA) an inferior wedge

studies were felt by both observers to be technically inadequate due to breakdown of the tagged MAA resulting in high background levels These five studies were deleted from the initial 82 patients studied, leaving 77 patients for analysis Statistical analyses were performed with the Student s t test for unpaired data and reported as the mean ± one standard deviation of the series *

Results

The normal myocardial image Three normal resting images are presented in Fig 1 The resultant image is dependent upon which coronary arteries are injected (Fig 1) and the coronary anatomy Injection of the left coronary artery (LCA) alone shows uniform distribution in the myocardium supplied by the LCA Normally the LCA injection appears much like the image of the left ventricle as seen by angiography, with a small inferior defect representing the right coronary artery (RCA) supply to the inferior diaphragmatic left ventricle The RCA injection appears as a ball of activity representing flow to the inferior diaphragmatic left ventricle with a much less dense tail representing flow to the right ventricle When both arteries are injected the left ventricular myocardium appears uniformly active and there is a faint visualization of the right ventricular myocardium (lower images Fig 1)

Fig 2 illustrates the basic pattern of myocardial images in the left anterior oblique (LAO) view with the regions of arterial distribution overlaid on a diagram of the normal coronary arteriogram It can be readily appreciated that in this view the left anterior descending (LAD) supplies an anterior septal wedge, the circumflex a posterior lateral wedge, and the RCA a smaller inferior diaphragmatic wedge The LAO view, which visualizes the heart from the apex toward the base, is the single best view for determining which areas of myocardium are abnormally perfused

The abnormal myocardial images Abnormal myocardial images demonstrate areas of diminished activity corresponding to areas of decreased blood flow Three typical examples are presented in Fig 3 Fig 3 (left) shows a patient with an anteroseptal infarction due to complete occlusion of the left anterior descending coronary artery Fig 3 (center) illustrates the image pattern resulting from an RCA occlusion with inferior infarction An inferior defect is seen and intense activity in the right ventricle is also present due to the RCA occlusion Fig 3 (right) shows a posterior lateral defect due to complete circumflex occlusion with infarction

Myocardial image correlations Overall 41 patients had perfusion defects and 36 patients demonstrated normal uniform myocardial perfusion The majority of patients in both groups (40/41, 34/36) had angina pectoris Three of five patients with the syndrome of pre infarction angina had image defects

Twenty two patients were classified as having no myocardial infarction 17 as possible 8 as

* Since in most cases only one coronary artery was injected there were five cases in which the arterial bed involved by definite infarction was not imaged These five cases (two patients with infarction in the left coronary system in whom only the right coronary artery was injected and three patients with inferior infarctions with dominant right coronary arteries in whom the left coronary artery was injected) were eliminated from the comparative analysis of image data versus ECG history of infarction and hemodynamic data since the area of known abnormality was not imaged

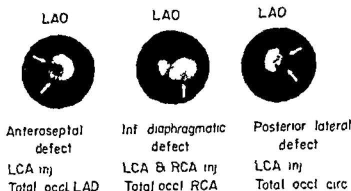


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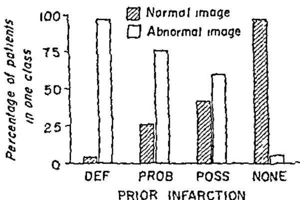


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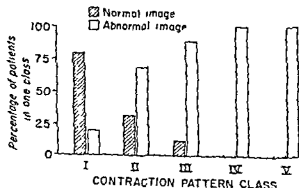


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LCA INJECTION
JA 20-87-42

LAD 100%
CIRC 90%
RCA 100%

AUTOPSY 8 x 10 cm SCAR

RAO

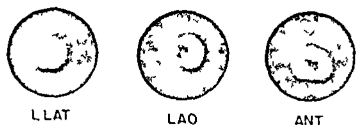


Fig 6 Myocardial perfusion image showing marked decrease in activity anteriorly (LAO view) and antero apically (L LAT and RAO) Patient had an 8 by 10 cm antero septal subendocardial infarction with 1 5 by 1 5 cm transmural apical infarction at autopsy Abbreviation *RAO* right anterior oblique

Table I The relationship between myocardial perfusion imaging and coronary anatomy

Coronary anatomy by per cent diameter stenosis (all patients)	*No of patients with normal scan*	*No of patients with abnormal scan*	*Per cent with abnormal scan*
0	13	0	0
1 50	6	0	0
51 75	7	2	22
76 99	6	10	62
100	4	29	88
Total	36	41	

Each patient was considered to have four coronary arteries—the left anterior descending right circumflex and posterior descending If more than one stenosis was present only the most severe lesion was considered For left coronary images only stenoses of its arterial system the left anterior descending and circumflex are tabulated for right coronary images only stenoses of the right and posterior descending coronaries are tabulated

the defects found on imaging (Fig 6) Two patients underwent aneurysmectomy each had extensive transmural scarring confirmed by histology which corresponded to image defects (Table II)

Comparison of the myocardial perfusion image with the presence or absence of myocardial scarring by direct visual inspection and palpation at the time of surgery was possible in 21 cases (Table II) Eight patients had normal images At surgery seven patients were felt to have normal ventricles and one patient had a region of paradoxical motion without scarring In thirteen patients with abnormal perfusion images nine had transmural scarring corresponding to the image defect at surgery, one had only hypokinesis in the region of the image defect, and three were normal

In toto 41 patients had myocardial image defects Thirty seven of these 41 (90 per cent) had evidence for prior myocardial infarction based on clinical history (30 patients classed as definite or probable) ECG Q waves (27 patients) local contraction pattern abnormality (23 patients Grades III IV or V contraction pattern) or direct surgical (nine of 13 patients operated) or histologic (four patients) identification of scar either singly or in combination

Thirty one* patients had normal myocardial images Three (10 per cent) had evidence for prior infarction based on clinical history (three patients classed as probable or definite) ECG Q waves (one patient) or local contraction pattern abnormalities (two patients Grades III IV or V) Of the eight patients undergoing surgery in this group none had an identifiable scar

Discussion

Considerations of the technique This technique is based on the principle that small particles (25 to 40 μ diameter) will lodge in the capillaries or precapillary arterioles of the vascular bed injected in a distribution corresponding to relative regional blood flow[8] When blood flow to a region is decreased as in experimental myocardial infarction from coronary occlusion the number of particles delivered to that region is reduced and a scan defect is created The safety of the technique has been established[11] Incomplete mixing of the particles is a potential problem with direct intracoronary injection however histologic examination of canine hearts following intracoronary MAA has shown particle distribution to be uniform[7] Poe[13] described nonuniform distribution of intracoronary MAA compared to a soluble indicator ^{131}Cs by in vitro sample counting The minor inequalities in flow distribution shown in that study were not of sufficient magnitude to be detected by external imaging In a single case in this series the coronary catheter selectively entered either the left anterior descending or

Same footnote as on page 10

Table II The relationship between myocardial imaging and surgical findings

Type of image	*Location of defect in image*	*Description of left ventricle at surgery*
I Normal perfusion images		
LCA (7 patients)	No defect	Normal
LCA (1 patient)	No defect	Anterior paradox (no scar)
Total 8		7 Normal 1 Anterior paradox
II Abnormal perfusion images		
LCA (VS)	Antero lateral apical defect	Extensive anterolateral transmural scar (aneurysm resected)
LCA (AR)	Antero infero apical	Infero lateral transmural scar
LCA (CE)	Infero lateral	4 by 7 cm recent transmural posterior myocardial infarction
LCA (VB)	Postero lateral defect	Infero lateral scar
LCA & RCA (MH 2 studies)	Infero lateral defect on LCA scan RCA scan normal	Small inferior scar
LCA (HA)	Extensive anterior defect	Large anterior transmural scar
LCA & RCA (HW)	Inferior defect with hang up of activity in proximal RCA	Inferior wall hypokinesis without definite transmural scar
LCA & RCA (RP)	Inferior defect with hang up activity in proximal RCA	Numerous punctate inferior transmural scars
LCA & RCA (VC)	Anterolateral	Transmural anterolateral aneurysm (resected)
LCA (JB)	Anteroseptal	Antero apical transmural scar
LCA (RG)	Apico inferior	Normal
LCA (EJ)	Infero lateral	Normal
LCA (FE)	Postero lateral	Normal
Total 13		9 Transmural scar 1 Region of hypokinesis 3 Normal

Abbreviations LCA, left coronary artery RCA right coronary artery
Pre-infarction angina

circumflex coronary artery resulting in an apparent perfusion defect This selective injection was recognized by angiography Jansen and co workers have also noted this phenomenon identifiable by streaming of angiographic dye in a small percentage of patients Further validation of this technique is provided by the normal regional perfusion demonstrated in all cases with normal coronary arteries in the current study We have also studied 15 patients without significant coronary lesions both at rest and with a second MAA injection during stress All of these patients had an identical normal perfusion pattern in both studies (unpublished data)

The radioactive particles used in this study (^{113m}In or ^{99m}Tc MAA) were prepared specifically for intracoronary injections with strict control of particle size number and specific activity MAA particles rather than commercially available human albumin microspheres were used primarily because they were more easily tagged with ^{99m}Tc and ^{113m}In and retained the radionuclide tag more satisfactorily The use of both ^{99m}Tc and ^{113m}In allows a second imaging study following stress[1] Injection of a single coronary artery rather than both coronary arteries necessitates knowledge of the presence or absence of collateral flow from the noninjected vessel and a knowledge of the dominance of the coronary system (i e an image with a perfusion defect of the inferior left ventricle was compatible with either normal perfusion of this region from a dominant right coronary system or decreased perfusion from a dominant the left coronary system) If one isotope is used for the LCA and a second for the RCA this problem can be obviated However this precludes use of the second isotope following stress Of the 64 patients with single vessel injections in this series five did have minor collateral flow from the noninjected to the injected vessels While this may increase the apparent magnitude of the perfusion defect autopsy correlation in one of the five patients showed close correlation between the size of the scar and the image perfusion defect (Fig 6)

Clinical value of the technique The data presented support the concept that image defects correlate primarily with the presence of myocar

dial scar. This was most conclusively shown by direct surgical inspection and histologic examination. Further evidence of previous infarction in the group with abnormal images was provided by clinical history, Q waves on ECG, contraction pattern abnormalities, and decreased ejection fraction.

The sensitivity of the technique for detecting myocardial infarction in humans is unknown. Experimentally, infarctions of more than 1.5 square cm are detectable.[17,18] One of the autopsy cases in the present series showed an inferior scar of 1.5 by 1.5 cm which was readily identified as an abnormality on myocardial image. One patient in this study had had a definite infarction by history and ECG which was not detectable by imaging. Surgical inspection showed only paradoxical motion and no scar; this infarction was presumably beneath the resolution of the technique and thus not visualized.

Compared to the ECG, the presence of a perfusion defect on the myocardial image was more sensitive than the presence of Q waves in diagnosing infarction. We have previously demonstrated that nearly all patients with clearly abnormal contraction patterns (Grades III, IV, and V) had previous myocardial infarction.[5] Imaging demonstrated regional perfusion defects in the majority (23/25) of this group. Seventeen patients with abnormal myocardial images had either normal (I) or only borderline (II) contraction abnormalities. Thirteen of the latter group had clinical, ECG, or surgical evidence of prior infarction, suggesting that the presence of a perfusion defect is more sensitive in detecting infarction than is the ventriculogram in this subgroup.

Four patients in this series demonstrated myocardial perfusion defects which could not be related to previous infarction by any of the criteria examined. Three of these patients had pre-infarction angina and no evidence of infarction was detected at surgery. These patients may represent a subset of patients who have resting perfusion defects in the absence of frank infarction. The other patient in this series with a perfusion defect and no other evidence of infarction had a distal complete circumflex occlusion. Whether this represents a false positive scan of an infarction undetected by other techniques is uncertain.

The presence of a high grade coronary stenosis or complete occlusion was not always associated with a perfusion defect. Conversely, less severe stenosis associated with other evidence of infarction produced perfusion defects. The close relationship of previous infarction and an abnormal perfusion image is in agreement with the data of Weller and co-workers[9] and Jansen and co-workers,[14] with the notable exception that perfusion defects were detected in some patients with pre-infarction angina in the present study. The results of this study differ from those of Ashburn and co-workers,[19] who found abnormal images in all patients with a 75 per cent or greater coronary artery stenosis. However, in their 22 abnormal images all but three were reported as having ECG evidence of myocardial infarction.

Gander and co-workers[7] have provided preliminary data suggesting that patients with myocardial perfusion defects are unlikely to show improved ventricular performance following revascularization. Our findings are in agreement with that study in that image defects were associated mainly with localized scar due to infarction—a situation unlikely to be improved by revascularization.

The ECG, ventriculogram and coronary arteriogram detect regional myocardial ischemia and scar only indirectly. Myocardial imaging, which visualizes relative regional coronary blood flow, provides a more direct method for the detection of regional myocardial ischemia and scarring. Although speculative at present, this information could provide a more rational basis for the selection of patients for revascularization surgery.

Summary

Scintillation camera myocardial perfusion images were performed in 77 patients with proved or suspected ischemic heart disease following the intracoronary injection of 1.5 mCi ^{99m}Tc or ^{113m}In macroaggregated albumin. Perfusion images were classified as normal (36) or abnormal (41) and the location of abnormality was noted. Thirty-seven out of 41 patients with abnormal images had prior myocardial infarction based on history (30), ECG Q waves (27), local contraction pattern abnormality (23), or direct surgical (9) or histologic (4) inspection either singly or in combination. Three out of five patients with pre-infarction angina had image defects—none had evidence of infarction by ECG, ventriculogram, or surgical inspection. Coronary artery stenosis correlated with image defects to the extent that myocardial infarction

was associated 28 out of 29 patients with total occlusions and other evidence of infarction had image defects four patients with complete occlu sions but without other evidence of infarction had normal images

We conclude that excepting patients with pre infarction angina this technique is more sensitive and direct in the identification of myocardial scar than standard ECG clinical evaluation or bi plane left ventriculography

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Table I Individual clinical and angiographic data

Subject	Age (yrs)	B.S.A	Frequency of angina	Exercise workload in kpm/min which produced angina	Electrocardiogram	Coronary lesions*	Angiographic severity of CAD†
1	47	1 86	Rest pain	150	Inferior infarction	5 232	8
2	51	1.88	< 1/day	450	Anteroseptal infarction	50,215	15
3	53	1 0	< 1/day	750	Inferior infarction	53 423	15
4	53	2 10	2 3/day	750	Left anterior hemiblock	3-4 111	7
5	48	1 92	1/day	300	Anterior wall infarction	415,323	15
6	42	2 31	5 6/day	150	Normal	404 135	16
7	46	1 2	1 2/day	450	Normal	304 130	10
8	48	1 98	1/day	300	Nonspecific ST T abnormalities	425 132	12
9	5	2 00	1/day	300	Anterior infarction	504 444	21
10	56	12	1/day	300	Nonspecific ST T abnormalities	534 433	22
11	44	2 10	3/day	600	Anteroseptal infarction	225 141	9
12	54	1 9	2/day	600	Inferior infarction	314 344	18
13		2 24	Rest pain	150	Inferior infarction	514 15	19

*The coronary artery obstructions are graded 0 to 5 (see Methods) and presented in the sequence right coronary artery left main trunk left anterior descending left circumflex left marginal branch and posterolateral branch
†See Methods.

heart failure and none was receiving digitalis One patient had mild hypertension but was not receiving any therapy All patients had a 75 per cent or greater obstruction in the left anterior descending artery

Procedure All long acting coronary vasodilators were discontinued 12 hours prior to the study Propranolol was stopped a minimum of 24 hours preceding catheterization Secobarbital (Seconal) 100 mg was administered prior to the catheterization which was performed in the postabsorptive state A Zucker bipolar pacing catheter was introduced through a right antecubital vein into the right atrium A No 7 Eppendorf catheter was positioned in the left ventricle The special thermistor coronary sinus catheter was positioned in the great cardiac vein via a left antecubital vein Pressures were measured using a Statham P23Db pressure transducer and recordings were obtained using either a Hewlett Packard Polybeam photographic recorder or an Electronics for Medicine DR 8 recorder Zero reference pressure was at the midchest level Electrocardiographic Leads V and aV_F were monitored throughout the procedure Cardiac output was determined by the indicator dilution method using indocyanine green Curve area was calculated by the Williams method The great cardiac vein blood flow was determined by the thermodilution method of Ganz and co workers[7] The special catheter was advanced as far as possible into the coronary sinus in order to maintain a stable position within the great cardiac vein In patients Nos 4 and 11 the catheter could not be advanced beyond the coronary sinus position but was stable at that site Catheter position was assessed by hand injection of Renografin 76 In order to verify catheter stability its location was filmed at rest after pacing and after exercise Dextrose 5 per cent in water at room temperature served as the indicator and was infused with a Harvard infusion pump at 38 2 c c per minute for 30 seconds Amplifier sensitivity was adjusted to provide 1 cm recorder deflection per 1 C Postinfusion body temperature was used as the baseline Venous flow in cubic centimeters per minute was calculated as outlined by Ganz and co workers The venous flow measurement from the great cardiac vein represents the venous outflow from the anterolateral myocardium

After basal observations were completed atrial pacing was instituted at 100 beats per minute After two minutes of pacing the left ventricular pressure cardiac output and great cardiac vein blood flow were measured The rate was then increased by 10 beats per minute every two minutes with the above measurements repeated every other rate increment and again with the onset of angina pectoris Pacing was then terminated and left ventricular pressure recorded as sinus rhythm returned Ten minutes after the atrial pacing test the patient was placed in the

Cardiac venous blood flow in atrial pacing versus exercise-induced angina pectoris

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Increases in myocardial oxygen demand in normal humans are fulfilled not by extracting more oxygen but via an augmentation of coronary blood flow[1] This normal response to increases in myocardial oxygen demand is limited by obstructive lesions in some symptomatic coronary artery disease patients Consequently an increased oxygen extraction sometimes takes place when the myocardial oxygen needs exceed the oxygen delivery capacity of the abnormal circulation[1] However this latter mechanism is not a major compensatory mechanism because of the already wide arterial venous O_2 difference which normally exists across the coronary vascular bed Therefore the capability to uniformly increase coronary blood flow in response to increasing myocardial oxygen needs remains a major factor governing a patient s response to increasing myocardial stress

Patients with stable angina pectoris develop pain or ischemic electrocardiographic changes at a reproducible level of myocardial stress[2-4] The myocardial oxygen demand is apparently adequately reflected by either the tension time index or the systolic blood pressure-heart rate product since in a specific patient pain generally occurs at a reproducible index level Since the index level is similar despite differing types of stress and differing hemodynamic response[3,4] the assumption is that the flow limitation is also independent of the type of myocardial stress applied Verification of this concept has had to await the development of a convenient and safe technique for quantitating coronary blood flow

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Clearance techniques for coronary blood flow measurements have been subject to criticism since a uniform distribution and clearance of the labeled tracer cannot be assumed in the face of coronary artery obstructions This may account for the considerable discrepancey in the reported coronary blood flow response to the stress of atrial pacing in coronary disease subjects[5,6] Ganz and co workers have recently introduced a thermodilution technique for measuring cardiac venous blood flow and have found resting values of coronary blood flow similar to those reported for other methods in normal subjects This technique utilizes a special thermistor catheter which can be advanced into the great cardiac vein and thereby regional myocardial venous blood flow can be measured

Utilizing the above approach, in conjunction with atrial pacing as a myocardial stress we have been able to quantitate limitations in cardiac venous outflow from the anterolateral myocardium of patients with angina pectoris[8] In order to determine whether in anginal patients the coronary flow limitation is comparable regardless of the type of myocardial stress we have measured the great cardiac vein blood flow response during angina pectoris induced by both atrial pacing and supine exercise

Methods

Case material (Table I) Thirteen patients with angina pectoris underwent measurements of great cardiac vein blood flow at rest with atrial pacing and during exercise Angina pectoris was induced by both pacing and exercise in all subjects All patients had sufficient symptoms to be considered as possible surgical candidates and the frequency of their angina pectoris had been stable a minimum of six weeks Eight patients had had prior myocardial infarctions and five had had only angina pectoris No patient had clinical

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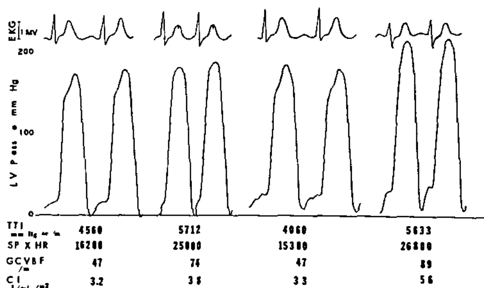


Fig 1 A retracing of hemodynamic data from a typical study is illustrated Initial resting observations are at the left As shown in the next sequence atrial pacing at a rate of 132 beats per minute resulted in angina pectoris ST segment depression in Lead V and an increase in great cardiac vein blood flow The third observation is ten minutes after terminating atrial pacing and with the patient in the feet up position prior to exercise Note that the hemodynamic values are similar to the original control observations Supine exercise as shown at the right also produced angina and in contrast to pacing the systolic pressure increased significantly and the heart rate was only 121 beats per minute The left ventricular end diastolic pressure is markedly elevated In this subject great cardiac vein blood flow increased somewhat more with exercise versus pacing induced angina *EKG* electrocardiogram *C I* cardiac index *G C V B F* great cardiac vein blood flow *L V* left ventricular *S P* × *H R* systolic pressure × heart rate and *T T I* tension time index

tion the measured increase in great cardiac venous blood flow would appropriately reflect the limitation of coronary blood flow to the anterolateral wall On the other hand if the ischemic pain originates from the inferior wall and if the flow to the anterolateral wall were normal the great cardiac vein blood flow would be expected to increase normally and consequently the degree of limitation of coronary blood flow to the inferior wall could be underestimated

Underlying the above analysis are several important assumptions first although increases in myocardial oxygen demands are not necessarily uniform throughout an abnormal ventricle the directional changes are similar and second that at least to the point of angina pectoris total coronary blood flow in one region of the myocardium does parallel the changes in myocardial oxygen demands in that area In support of these concepts Yoshida and co workers[9] using the thermodilution technique to measure coronary sinus blood flow and Holmberg[4] utilizing the xenon clearance technique for coronary blood flow measurements have shown that coronary blood flow does indeed increase in coronary disease patients in proportion to increasing myocardial oxygen demands However subjects with coronary artery disease cannot increase coronary venous outflow to the same degree as normal subjects and if their myocardial oxygen requirements are further increased above the anginal threshold additional increases in coronary flow may not occur[1,9] More recently, Maseri and co workers[5] have presented xenon washout studies which suggest an actual reduction in coronary blood flow in the ischemic zone during a myocardial stress which *exceeds* the angina threshold Although a redistribution of coronary blood flow may occur under such circumstances it has not yet been convincingly shown that coronary blood flow fails to increase in response to increasing myocardial oxygen demands short of the angina threshold Therefore the measurement of great cardiac vein blood flow at the very onset of angina should provide a useful evaluation of the overall anterolateral coronary blood flow at that time

Results

A typical study is illustrated in Fig 1

Significant differences are present in the hemodynamic parameters associated with pacing

feet up position and the hemodynamic measurements were again determined Supine exercise was then performed at a workload which had produced angina during an exercise test the prior day With the onset of angina, the left ventricular pressure cardiac output, and great cardiac vein blood flow were measured and the exercise terminated

After hemodynamic studies were completed coronary arteriograms were performed by the Sones technique with either a six inch or 6 to 9 inch intensifier and 35 mm film A left ventriculogram was photographed in a 20 degree right anterior oblique projection

Left ventricular end diastolic pressure was measured at the intercept of the down slope of the a wave and the upstroke of the left ventricular pressure and averaged for ten beats Left ventricular area, in millimeters of Hg in seconds was planimetered The left ventricular area was defined as the area under the left ventricular pressure curve beginning with the onset of ventricular contraction and ending when the left ventricular pressure falls below the end diastolic pressure The tension time index was calculated as the product of left ventricular area times heart rate The product of systolic blood pressure and heart rate was also determined An expression of the left ventricular stroke work index in gram meters per square meter was calculated as

Left ventricular stroke work index = stroke index × (left ventricular systolic pressure − left ventricular end diastolic pressure) × 13 6/1 000 Left ventricular minute work = left ventricular stroke work index × heart rate

Coronary artery lesions were graded as follows 0 = no disease 1 = 30 per cent obstruction 2 = 30 to 50 per cent obstruction 3 = 50 to 75 per cent obstruction, 4 = 75 to 99 per cent obstruction and 5 = total occlusion The right coronary artery main trunk of the left coronary artery the anterior descending artery the left main circumflex the left marginal branch, and the left posterolateral branch of the circumflex artery were each individually graded according to its most severe lesion The overall severity of coronary artery disease was then defined as the sum of the obstruction grades of each vessel grades 1 and 2 lesions were excluded from this sum representing overall severity since these lesions have little relationship to clinical manifestation of coronary disease

The significance of observed differences was determined by the paired t test

Exercise testing Progressive exercise testing was performed the day prior to catheterization in order to determine the workload which produced angina pectoris This test was carried out on a bicycle ergometer in the upright position In eleven out of thirteen patients the ergometer used for the initial testing was also utilized during the catheterization study in order to avoid the problem of equal ergometer calibration Subjects were in the postabsorptive state Bipolar chest leads equivalent to Leads V_4 V_5 and V_6 and also the brachial artery pressure were monitored throughout the test Exercise was started at 150 k p m and maintained for three minutes following which the subject rested for two minutes The workload was increased by 150 k p m increments using the above exercise rest sequence The test was terminated when the patient experienced chest pain similar to his usual angina pectoris or developed horizontal ST segment depression equal to or greater than 1 mm This final work load was utilized as the exercise stress during the hemodynamic study

Critique of methods The measurement of great cardiac vein blood flow estimates coronary blood flow to the anterolateral left ventricular myocardium The measured venous outflow includes not only the venous drainage from the anterolateral coronary arteries but also the venous return from any collateral flow to the anterolateral myocardium from more remote vessels However this method does not provide any data on the relative rates of perfusion of the epicardial versus subendocardial regions nor does it define whether there is uniform perfusion throughout the anterolateral myocardium It simply provides an accurate and rapid technique for assessing total coronary flow to one large myocardial region

Use of the method described above in conjunction with a myocardial stress test allows one to make an estimate of ability to increase coronary blood flow However it should be emphasized that this assessment of flow reserve does not imply that an observed limitation is necessarily from the anterolateral myocardium As either the atrial pacing test or the multistage exercise is performed the myocardial stress is not further increased after the onset of pain The pain could originate from ischemia of either the inferior or anterolateral myocardium In the latter situa

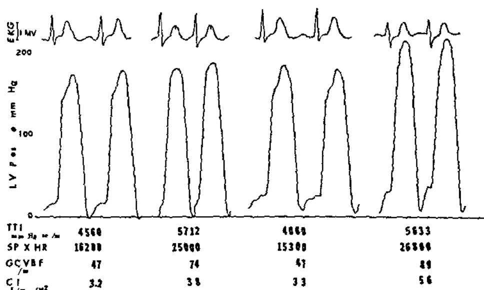


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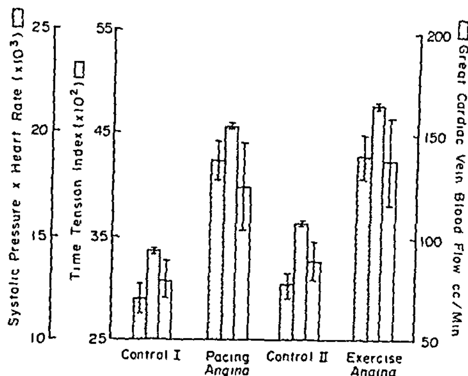


Fig 2 There are no significant differences in the indices of myocardial oxygen demand at the onset of angina pectoris whether pacing or exercise induced The great cardiac vein blood flow was also similar during pacing or exercise induced angina

Table II Summary of hemodynamics associated with angina pectoris induced by pacing and exercise

	Control I	Pacing angina	Control II†	Exercise angina	P value Exercise versus pacing
Heart rate	80 ± 3*	118 ± 4	80 ± 3 5	107 ± 4	0 01
Systolic pressure (mm Hg)	151 ± 6	160 ± 6	160 ± 4 5	178 ± 6	0 01
LVEDP (mm Hg)	18 ± 3	19 ± 3	23 ± 2 8	38 ± 2	< 0 001
Cardiac index (liters/min /M)	3 3 ± 0 2	3 5 ± 0 2	3 3 ± 0 2	4 6 ± 0 4	0 02
TTI (mm Hg sec /min)	3 368 ± 182	4 637 ± 187	3 697 ± 151	4 871 ± 192	ns
SP × HR	12 000 ± 700	18 900 ± 1 000	12 900 ± 600	19 200 ± 1 200	ns
Stroke index (c c /M²)	42 ± 3	30 ± 3	41 ± 1 9	43 ± 3	0 01
LVSWI (g m/M)	73 3 ± 4 3	56 9 ± 5 3	75 1 ± 3 8	77 7 ± 6 7	0 03
LVMW (g m/M)	5 920 ± 450	6 700 ± 690	6,260 ± 500	8 490 ± 930	0 02
GCVBF (c c /min)	80 ± 10	129 ± 22	90 ± 10	141 ± 23	ns
LV dp/dt (mm Hg/sec)	1 511 ± 70	1 842 ± 88	1 528 ± 83	1 938 ± 109	ns

GCVBF great cardiac vein blood flow LV dp/dt maximum rate of rise of ventricular pressure LVEDP left ventricular end-diastolic pressure LVMW left ventricular minute work LVSWI left ventricular stroke work index SP × HR systolic pressure × heart rate and TTI tension time index
*± S E M
†Feet up prior to exercise

versus exercise induced angina pectoris and are summarized in Table II All subjects had a higher systolic pressure during exercise versus pacing induced angina, although a systolic pressure rise also accompanied pacing induced angina pectoris in ten subjects The heart rate at the onset of angina was significantly higher with pacing Left ventricular dp/dt rose similarly during pacing and exercise Ischemic left ventricular dysfunction as evidenced by either an exercise increase in left ventricular end diastolic pressure or its failure to fall during pacing was demonstrated in all subjects during exercise and in all but two patients during pacing Both cardiac index and left ventricular minute work increased significantly during exercise yet did not show any important changes with pacing

Fig 2 illustrates that the tension time index and the systolic pressure heart rate product were similar at the onset of angina whether it was pacing or exercise induced The correlation coefficient for the tension time index at the onset of pacing versus exercise induced angina was r=0 79 and for the systolic pressure heart rate

product it was r=0 69 both are significant at the 1 per cent level

The level of great cardiac vein blood flow was comparable at the onset of either pacing or exercise induced pain (Fig 2) Although in nine patients the great cardiac vein blood flow was higher during exercise the difference as determined by the paired t test was not significant (p=0 10) The higher flow during exercise could not be correlated with either the site of a prior infarction or the coronary anatomy All patients had some increase in great cardiac vein blood flow with increasing myocardial stress At the anginal threshold only three patients exhibited an approximate doubling of flow and the remainder generally had flow increases of less than 50 per cent above the resting level

Electrocardiographic monitoring revealed ST segment depression equal to or greater than 1 mm in nine subjects and the degree of depression was the same during both pacing and exercise

Discussion

The purpose of the present study was to determine if in a given patient angina pectoris developed at similar levels of regional coronary blood flow whether the pain was induced by atrial pacing or supine exercise Our data show that despite the marked differences in the associated hemodynamic responses to these differing stresses angina pectoris develops at comparable levels of great cardiac vein outflow This implies that it is the limitation in coronary blood flow rather than the type of myocardial stress that governs the level of myocardial work at which ischemic pain and left ventricular dysfunction appear It is postulated that a patient with angina pectoris cannot increase his regional coronary blood flow above an observed level without developing angina pectoris The fact that all patients had some increase in great cardiac vein blood flow in response to pacing and exercise implies that angina was not secondary only to a redistribution of a fixed coronary blood flow There remained some potential to increase overall flow although angina developed at a point when only modest increases in cardiac venous flow had occurred Since all the subjects had significant obstructions in the left anterior descending artery it is likely that we were measuring a flow limitation to the anterolateral myocardium However we cannot exclude the possibility that we were simply measuring a normal coronary flow response to two hemodynamically different stresses We again emphasize that our data do not provide any information regarding a possible redistribution of coronary blood flow as an additional important factor contributing to the onset of angina

Some subjects exhibited a slightly greater increase in great cardiac blood flow during exercise than during pacing One possible explanation is that the exercise load selected to induce angina was based on a prior upright bicycle test The myocardial stress at the same external work load may be somewhat greater in the supine position because of the increased systemic resistance and venous return in this position Therefore the myocardial stress induced by exercise may have slightly exceeded that which was required to induce angina and so caused a further increase in coronary blood to adequately perfused regions within the territory served by the great cardiac vein

It is important to note that we did not attempt to achieve a prolonged steady state for the hemodynamic measurements during either exercise or pacing induced angina Although it has not been specifically studied in man one doubts that a true steady state (often defined as no significant hemodynamic alterations over a three minute observation period) can be easily maintained during supine exercise induced angina—despite a constant external workload The patient s reaction to the pain the changing arterial pressure and the probable changes in left ventricular volume all contribute to the unsteadiness of exercise induced angina Consequently we chose to measure great cardiac vein blood flow within the first 30 seconds after the onset of angina whether pacing or exercise induced in order to look at venous outflow at a specified point in time within the symptom complex For this type of study the thermodilution method is uniquely suitable since the brief response time of the thermistors provides a method capable of detecting flow changes occurring over a time period of only several seconds—a feature not available in any other method currently used to assess coronary blood flow During our 30 second observation period there were no significant changes in great cardiac vein blood flow At least for that brief interval a reasonably steady state was achieved

It is apparent that both exercise and atrial pacing effect a myocardial stress suitable for measuring the coronary blood flow reserve since

the levels of great cardiac vein blood flow are similar at the onset of angina with the use of either method However, some of the differences of these stresses should also be emphasized Exercise more dramatically illustrates the degree of left ventricular dysfunction because the ischemic ventricle must function in the face of greater pre and afterloads Such exercise hemodynamic changes would seem to be related to the patient s response to the stresses of daily living Measurement of the maximal exercise also provides more useful information in the functional evaluation of patients with coronary artery disease Atrial pacing with rates of up to 150 beats per minute is capable of doubling coronary flow both in man[11] and dogs[12] but further increases in myocardial oxygen demand and coronary blood flow are not likely to be attained with pacing Thus atrial pacing may not produce myocardial ischemia in some patients with coronary artery disease In contrast to pacing exercise can triple coronary blood flow[11,13,14] and also is more likely to elicit an ischemic response in coronary disease patients[11] Furthermore in selecting a myocardial stress for the clinical evaluation of patients one would like the level of stress which produces myocardial ischemia to provide some predictive information relative to the coronary blood flow reserve Here again exercise appears to be of greater value since the paced heart rate at the onset of angina is only a fair guide to the limitations of great cardiac venous blood flow whereas the maximal exercise capacity bears a more direct relationship to the ability to increase great cardiac vein blood flow[8]

Summary

Thirteen patients with angina pectoris underwent measurements of great cardiac vein blood flow at rest with the onset of angina pectoris induced by atrial pacing and again during angina pectoris induced by exercise in order to compare the regional coronary blood flow response to differing myocardial stresses All patients had significant obstructions of the left anterior descending artery

Exercise induced angina compared to pacing induced angina was associated with a higher systolic pressure, higher left ventricular end diastolic pressure, and a lower heart rate Indices of myocardial oxygen demand, that is, the systolic pressure heart rate product and the tension time index, increased to a similar degree during both types of myocardial stress and great cardiac vein blood flow paralleled these changes

We conclude that in a given patient the level of regional coronary blood flow is similar at the onset of either pacing or exercise induced angina despite significant differences in the hemodynamic response to these myocardial stresses

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Circulating renin in essential hypertension an evaluation of its significance in the Japanese population

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It is now widely believed that renin plays an important role in the pathogenesis of renovascular hypertension malignant hypertension and renin producing tumor However there is no definite evidence that renin is involved in the etiology of essential hypertension Recently several laboratories in western countries have reported that twenty per cent of essential hypertension has relative low plasma renin activity (PRA) and fail to increase it normally in response to sodium restriction and standing These observations coincide with Conn s diagnostic criteria for the normokalemic primary aldosteronism[3] However most of the hyporeninemic patients have normal or low aldosterone secretion rates and no apparent hypokalemia was found in them[4] These findings suggest that essential hypertension with low plasma renin activity differs from primary aldosteronism Recently Laragh and coworkers have reported that in the hypertensive group with low renin level the occurrence of vascular complications is much less than in the other groups with high or normal renin levels

Some modern Japanese reports[6] have described that 50 to 60 per cent of essential hypertensive cases have low PRA levels and are hyporesponsive to the stimulus of renin secretion There seem to be significant differences in the incidences of low renin hypertension between western countries and Japan To re examine (1) the incidence of low renin hypertension in Japan and (2) the prognostic significance of plasma renin levels in essential hypertension plasma renin activity was measured in 200 patients with essential hypertension and in 139 normal control subjects

Materials and methods

Two hundred patients with essential hypertension and 139 healthy normotensive subjects were included in this study The normotensive individuals ranged in age from 11 to 81 years Fifty seven were men and 82 were women All hypertensive patients had a blood pressure of 150 mm Hg systolic and 90 mm Hg diastolic or higher on repeated observations Their ages ranged from 11 to 71 years One hundred thirty eight were men and 62 were women The diagnosis of essential hypertension was established by various examinations including history physical examinations routine laboratory tests intravenous pyelography radioisotope renography renoscintigraphy renal arteriography and determination of plasma 11 OHCS aldosterone and urinary catecholamines or vanillyl mandelic acid All patients were studied in Tohoku University Hospital or its affiliated hospitals Antihypertensive medication was discontinued at least two weeks before study and an unrestricted intake of sodium (approximately 250 mEq per day or above) was allowed for at least one week before plasma renin activity

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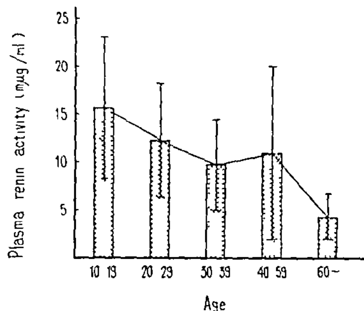


Fig 1 Relationship between PRA at rest and age obtained in 139 healthy control subjects

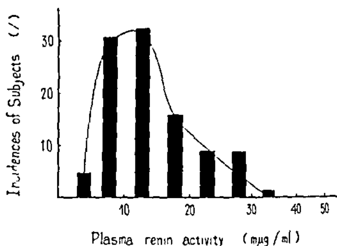


Fig 2 Frequency distribution of PRA at rest in 139 healthy subjects

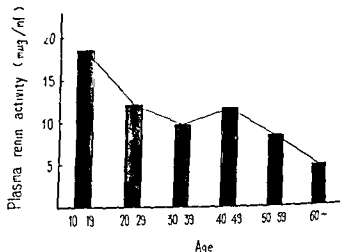


Fig 3 Relationship between PRA at rest and patients age obtained in 200 hypertensive subjects

measurement Sampling of blood was done with fasting patients kept in recumbent position for at least one hour in the morning To evaluate the reaction of renin secretion an intravenous injection of furosemide (1 mg per kilogram of body weight) and taking two hours upright posture were loaded

Plasma renin activity in peripheral blood was determined by a method using radioimmunoassay of angiotensin I [8]

One milliliter of plasma was incubated at 37° C at pH 5 5 for six hours with disodium ethylene diamine tetraacetic acid (EDTA) and diisopropyl fluorophosphate (DFP) The sample was then diluted tenfold with physiologic saline and heated in a boiling water bath for five minutes After centrifugation angiotensin I in the supernatant was assayed radioimmunologically This method was approximately four times more sensitive than Haber s method [9] The PRA values determined by the present method showed a good correlation with those of bioassay

Results

Resting peripheral vein blood PRA

Healthy subjects Peripheral vein blood PRA in 139 healthy subjects ranged from 2 to 36 mμg per milliliter (mean and SD 12 4 ± 7 3 mμg per milliliter) at rest Fig 1 shows the values of PRA at different ages The level of PRA in younger persons under 19 years of age was slightly higher than that in the other age groups On the contrary, the estimated values were very low in advanced ages over 60 years In the individuals from 20 to 59 years of age however, no significant differences in the PRA levels were found

To evaluate the normal values and variations of resting peripheral vein blood renin activity the distribution of PRA was examined in 119 normal subjects aged 20 to 59 Fig 2 illustrates the distribution of PRA's in this age group Ninety three per cent of the subjects (112 persons out of 119) had the values between 5 and 30 mμg per milliliter

Essential hypertension The estimated values of PRA in 200 patients with essential hypertension ranged from less than 2 to 100 mμg per milliliter with a mean and SD of 15 6 ± 18 8 mμg per milliliter Fig 3 shows the values of resting peripheral vein blood PRA in each age group As revealed in healthy persons the levels of PRA in essential hypertension was slightly high in young patients under 19 years of age and significantly low in older patients over 60 years of age

Table I Incidence of low normal and high PRA hypertension

PRA (mean ± S D) (mμg/mL)	Patients		Ratio of male to female			Age (mean ± S D) (yr)
	No	%	No		%	
Low PRA 25 ± 08	47	23.5	M	3?	68 1	37 0 ± 13 2
			F	15	31 9	
Normal PRA 1?6 ± 6 6	129	64 5	M	85	66 4	36 0 ± 1?0
			F	44	33 6	
High PRA 57 7 ± 23.5	24	12 0	M	21	87 5	34 0 ± 12 7
			F	3	12 5	

To compare the essential hypertensive with control subjects the distribution of the PRA values was examined (Fig 4) A significant deviation from the distribution pattern in healthy persons was found in essential hypertension The peak of the distribution curve in the control group was 12 5 mμg per milliliter while in the hypertensive group it was 7 5 In the latter PRA s were slightly low ranging from 2 to 20 mμg per milliliter It may be said that the resting PRA level in essential hypertension tends to be lower than that in healthy persons

Classification of essential hypertension Two hundred cases of essential hypertension were classified into three groups according to their resting values of peripheral vein blood PRA (Table I) Subnormal resting levels of PRA was found in 47 (23 5 per cent) out of 200 essential hypertensive subjects (low renin group) Thirty two were men and 15 were women The mean value and S D of PRA was 2 5 ± 0 8 mμg per milliliter with a range of less than 2 to 4 9 mμg per milliliter One hundred twenty nine cases (64 5 per cent) had normal resting PRA (normal renin group) Eighty five cases were men and 44 were women The PRA values ranged from 5 to 30 mμg per milliliter (mean and S D 12 6 ± 6 6 mμg per milliliter) The remaining twenty four patients (12 per cent) showed increased resting PRA s above normal (high renin group) Twenty one patients were men and three were women The PRA levels ranged from 31 to 100 mμg per milliliter (mean and S D 57 7 ± 23 5 mμg per milliliter)

In 138 male patients 23 3 per cent had low 61 5 per cent normal and 15 2 per cent high PRA levels In 62 female cases however low PRA values was found in 24 5 per cent normal in 70 5 per cent and high in 4 9 per cent There are no significant sex differences in these percentages except that the high renin level was more frequent in males than in females. Mean ages of three groups were 37 0 ± 13 2 in low 36 0 ± 12 0 in normal and 34 0 ± 12 7 in high renin groups

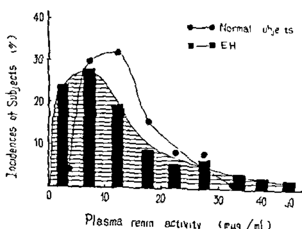


Fig 4 Frequency distribution of PRA at rest in essential hypertensive and control subjects (Solid circles indicate control subjects)

Clinical features in each group Fig 5 shows blood pressure creatinine clearance and retinal changes in three groups In this figure younger patients (less than 20) and elder ones (over 60) were excluded because of their deviation in PRA from normal as described above Mean values and S D of blood pressure were 174 ± 36 2/105 1 ± 16 4 mm Hg in the low PRA group 183 2 ± 29 8/108 3 ± 16 9 mm Hg in the normal PRA group and 178 3 ± 16 9/110 4 ± 22 8 mm Hg in the high PRA group There were no

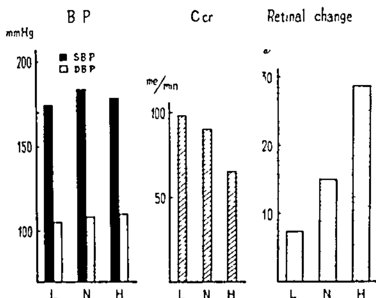


Fig 5 Clinical features in the three groups (L low PRA group N normal PRA group H high PRA group BP systemic blood pressure SBP systolic blood pressure DBP diastolic blood pressure Ccr creatinine clearance retinal changes per cent of patients who had KW III or IV)

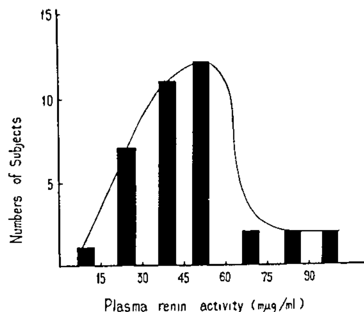


Fig 6 Frequency distribution of peripheral vein blood PRA after the stimulation in 37 healthy subjects

significant differences among the baseline blood pressure levels of these groups Regarding renal function however obvious differences were revealed between them The creatinine clearance was 65 1 ± 32 1 ml per minute in the high group 89 8 ± 22 6 ml per minute in the normal group and 97 8 ± 25 8 ml per minute in the low PRA group Renal function was almost normal in the low, but distinctly impaired in the high renin group Severe retinal changes (KW III or IV) were observed in 7 3 per cent in the low 15 1 per cent in the normal and 28 7 per cent in the high renin group

Provocation test for renin secretion

Healthy persons Provocation of renin secretion was studied in 37 healthy subjects aged from 20 to 52 years Twenty one were men and 16 were women The peripheral vein blood PRA values after the load of furosemide and upright posture was 48 9 ± 21 9 mμg per milliliter Fig 6 demonstrates the relationship between subject numbers and the PRA values Twenty nine cases out of 37 (88 per cent) had the PRA values of 15 to 60 mμg per milliliter and this range of PRA was defined normal in this study

Essential hypertension The provocation of renin secretion was done in 161 cases of essential hypertension One hundred sixteen were men and 45 were women Fig 7 shows the responses of renin secretion in essential hypertensive subjects of different ages After the stimulation the mean PRA values of 18 cases under 19 years increased from 16 5 ± 15 3 to 47 5 ± 35 5 39 cases aged 20 to 29 years increased from 15 1 ± 18 7 to 40 0 ± 32 1, 44 cases aged 30 to 39 years increased from 10 3 ± 9 3 to 27 1 ± 25 6 39 cases aged 40 to 49 years increased from 12 9 ± 21 1 to 30 1 ± 28 1 16 cases aged 50 to 59 years increased from 11 4 ± 10 6 to 19 6 ± 13 2, and 5 cases aged over 60 years increased from 5 0 ± 4 0 to 7 0 ± 4 8 mμg per milliliter respectively There was a gradual decrease in the renin secretion with aging

One hundred thirty eight cases aged from 20 to 59 years out of 161 cases given furosemide intravenously and kept upright were classified into three groups according to their responses in renin secretion (Table II) In 42 cases with low PRA, 81 per cent did not respond to the stimulus while the remaining 19 per cent responded normally On the other hand more than three fourths of patients with high PRA showed a hyper response to the stimulus In 105 cases of normal PRA hypo, normal and hyper response after load were observed in 32 4 53 3 and 14 3 per cent respectively In 59 nonresponders peripheral vein blood PRA did not significantly increase in the provocation In these nonresponders the mean values and S D were 4 8 ± 2 8 mμg per milliliter at rest and 7 6 ± 4 0 mμg per milliliter after the load The PRA values in 58 normal responders increased from 14 1 ± 10 1 to 33 8 ± 13 5 mμg per milliliter In 21 hyperresponders plasma renin levels

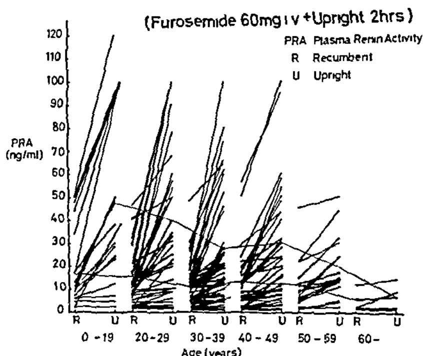


Fig 7 Reaction of PRA to the stimulation by intravenous furosemide and upright posture in 161 patients with essential hypertension

Table II Relationship between resting vein blood PRA and the responsiveness to the stimulus

	Low PRA		*Normal PRA*		*High PRA*		*Total*	
	No	%	*No*	%	*No*	%	*No*	%
Hyporesponse	34	81	34	32 4	0		68	42.2
Normal response	8	19	56	53 3	3	21 4	67	41 6
Hyperresponse	0		15	14 3	11	78 6	26	16 2
Total	42	100	105	100	14	100	161	100

increased markedly from 33 0 ± 25 8 to 84 2 ± 15 5 mμg per milliliter

The blood pressure creatinine clearance and retinal changes in hypo normal and hyper responders are illustrated in Fig 8 and Table III There is no significant difference in the average age between hypo responders and normal responders In hyper responders however the average age was lower than that of the other two groups No significant differences were recognized among baseline blood pressure levels and creatinine clearance in the three groups Severe involvement of ocular fundi (KW III or IV) was found in 14 per cent of the hypo responsive group 21 4 per cent of the normal responsive group and 10 per cent of the hyper responsive group From these results it is obvious that there are no correlations between the responsiveness of renin secretion and hyper tensive changes of cardiovascular renal organs

Discussion

The present study revealed that 23 5 per cent of patients with essential hypertension had low 64 5 per cent had normal and 12 per cent had high peripheral vein blood PRA levels at rest These results are in good accordance with that of Laragh[3] in which PRA values are subnormal in 27 per cent of patients within normal range in 57 per cent and increased in 12 per cent Regarding the incidence of low renin hypertension however there is a remarkable difference between our data and those of other Japanese investigators[6,7] This discrepancy may be caused by the difference in the methods used in each laboratory

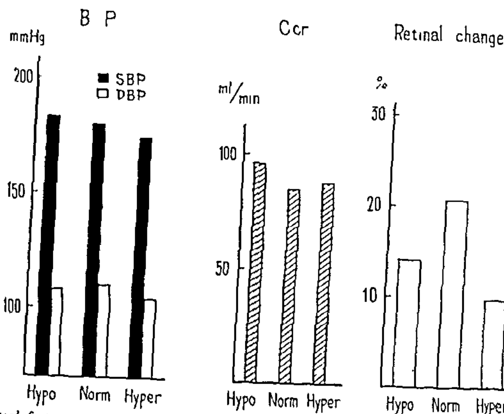


Fig 8 Clinical features in the three groups (Hypo hyporesponder Normal normal responder Hyper hyperresponder SBP systolic blood pressure DBP diastolic blood pressure Ccr creatinine clearance retinal change per cent of patients who had KW III or IV)

Table III Incidence of hypo , normal, and hyper responders

	mμg/ml	Patients No	Patients %	Age (mean ± S D) (yr)
Hyporesponder 4 8 ± 2 8 →	7 6 ± 4 0	59	42 8	38 2 ± 10 7
Normal responder 14 1 ± 10 1 →	33 8 ± 13 5	58	12 0	36 9 ± 10 1
Hyperresponder 33 4 ± 20 8 →	84 2 ± 15 5	21	15 2	31 1 ± 8 1

Recently Sealey and Laragh[10] have examined the commonly used radioimmunoassay methods of renin and found that commercial kits are inadequate to assay low levels of PRA because of too short an incubation time at nonoptimum pH and incomplete angiotensinase inhibition with dimercaprol and hydroxyquinoline which are less effective than DFP They have searched out the optimum condition for measuring plasma renin activity immunologically in low renin samples and reported that the most suitable condition consists of an 18 hours incubation at pH 5 7 and 37° C in the presence of EDTA, DFP and neomycin We had also pointed out previously the same problems in the procedure of renin estimation[8] and the present study was performed avoiding these pitfalls enumerated above To keep the reliability of the method, we estimated plasmas with known PRA values (5 and 30 mμg per milliliter) as reference standards in every measurement of unknown samples Our method was about 4 times more sensitive than Haber s method and able to detect subnormal PRA levels Haber s original method cannot estimate the subnormal PRA levels It is likely that high incidences of low renin hypertension reported from other Japanese laboratories came from an inadequate sensitivity of the methods of PRA measurement

On the pathogenesis of low renin hypertension many studies have been done in the world[11-14] Some of them have described that aldosterone secretion rates are normal or sometimes low, and not normally responsive to sodium depletion (low sodium or diuretica) The secretion rates of this hormone are also not suppressed normally by sodium load (high sodium diet or saline infusion) To explain this inappropriate secretion of aldosterone it has been supposed that the renin angiotensin aldosterone system is short circuited by

another mineralocorticoid Woods and co workers[14] observed an efficacy of aminoglutethimide an inhibitor of adrenal steroidogenesis to lower the blood pressure in patients with low renin hypertension and suggested that an as yet unidentified adrenal steroid might participate in the pathogenesis of low renin hypertension

What mineralocorticoids are involved in the etiology of low renin hypertension? Melby Dale and Wilson[1] have recently studied the secretion of 18 hydroxy deoxycorticosterone in essential hypertension They found that some patients with low PRA and low aldosterone secretion rates and marked increase in the secretion of this hormone On the other hand Spark and co workers[1 3] have described that an active metabolite having potent sodium retaining activity was produced from 18 hydroxy deoxycorticosterone when the adrenal cortex of the patient with low renin hypertension was incubated with 18 OH DOC These results suggest that the low renin hypertension may be a discrete fundamentally different hypertensive disorder but the exact pathogenesis of this hypertension remains to be elucidated in the future

Recently Brunner and co workers have claimed that plasma renin activity may be a useful index in distinguishing hypertensive patients with regard to risks from vascular complications They emphasized that patients with high or normal levels of plasma renin had a high incidence of stroke or myocardial infarction than patients with low renin levels although there are no significant differences in the degrees of hypertension between the three groups

On the contrary several investigators have reported that there was no relationship between the PRA level and the incidence of myocardial infarction and cerebrovascular accident [8] Mroczek Finnerty and Catt measured the PRA in 371 Black patients with essential hypertension in relation to the urinary sodium excretion according to the criteria of Laragh and made a retrospective study on the incidence of myocardial infarction and cerebrovascular accident They found that the incidence of such complications was identical in low normal and high renin groups However their data were derived from the retrospective studies on the Black hypertensive population in whom low renin hypertension was considered to be more common

Recently Doyle and co workers[1] reported a follow up study for five years describing that the plasma renin level was not related to the development of myocardial infarction and cerebrovascular accident In their report however there was marked difference in the mean ages between the patients with and without vascular complications Mean age of the former was 65 years while the latter was 50 years This age difference might have profound influence on the PRA levels of their patients The conclusion of Doyle and co workers must be re evaluated on the basis of the age factor

In our data hypertensive angiopathy in the ocular fundi and the kidney were very mild in patients with low PRA values at rest while a marked decrease in renal function and severe retinal changes were observed in the patients with high PRA values at rest However it is not clear whether vascular complication in the latter is caused by the high level of PRA or conversely high PRA level is originated by the hypertensive angiopathy in the kidneys We therefore could not conclude that plasma renin levels have a prognostic significance in essential hypertension

Summary

Plasma renin activity (PRA) was measured in 139 healthy subjects and 200 patients with essential hypertension There was an obvious relationship between the PRA levels and aging Elevated PRA values were obtained only in younger subjects under 20 years of age while the PRA levels were very low only in advanced ages over 60 years

In essential hypertensive subjects subnormal resting PRA was found in 23 5 per cent normal PRA in 64 5 per cent and high PRA in 12 per cent A marked impairment of renal function and severe retinal changes were observed in the patient with high resting PRA values On the contrary hypertensive complications of the kidney and ocular fundi were mild in the patients with low resting PRA values

A reaction of renin secretion was studied in 161 patients with essential hypertension There were no apparent relationships between the responsiveness of the renin system to intravenous furosemide following upright posture and hypertensive vascular injury

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Use of moving epicardial electrodes in defining ST segment changes after acute coronary occlusion in the baboon Relation to primary ventricular fibrillation*

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With the technical assistance of J Korrûbel H T S

In 1920 Pardee[1] related ST segment elevation of the standard leads of the electrocardiogram (ECG) to acute myocardial infarction In 1945 Wolferth and Bellet[2] described ST segment elevation and depression as primary and secondary events which they explained by systolic and diastolic currents but Nahum Hamilton and Hoff had shown in 1943 that ST segment changes in acute myocardial infarction were due to baseline shifts This finding was later confirmed elaborated and further explored by Katcher Pierce and Sayen[4] Samson and Scher[5] Prinzmetal and co workers and Taccardi[7] Although the exact nature of ST segment changes is still open to discussion Maroko and co workers [1] have recently suggested that absolute values of the average and maximal epicardial ST segment elevation and the number of sites involved 15 minutes after coronary artery ligation are directly proportional to the severity and magnitude of myocardial cellular damage and can be used to predict the severity of myocardial necrosis after 24 hours However the majority of patients with fatal acute myocardial infarction die from early rhythm disturbances frequently in the first hour Thus if ST segment changes were to have significant prognostic value for mortality such changes should be related to early fatal dysrhythmias

In previous work[12] we have shown that it is possible to predict correctly survival or primary ventricular fibrillation in baboons with acute coronary ligation during the first hour by using well defined ventricular dysrhythmias as warning signs In this study we examined relationships between epicardial ST segment changes and the early mortality of acute myocardial infarction as defined by the onset of primary ventricular fibrillation (VF) within the first hour after coronary artery occlusion in the baboon

Methods

Sixty healthy wild living Cape Chacma baboons (*Papio ursinus*) were anesthetized with phencyclidine HCl 1 25 mg per kilogram of body weight and pentobarbital (0 06 mg per kilogram per minute) A midsternal thoracotomy was performed and the distal third of the anterior descending coronary artery was ligated The heart was subsequently observed for one hour or until the onset of VF Detailed information on material and methods has been published [12] The mean body weight was about 21 kilograms and the mean size of the infarction about 10 per cent of the total wet heart weight of the heart cut 1 cm above the semilunar valves (Table I)

Four needle tipped electrodes were connected subcutaneously to the limbs and standard lead recordings were made on a modified Corbin Farnsworth S5EP with a direct graphic hot stylus recorder LGGR and an alternating current (ac) amplifier A unipolar epicardial electrogram was

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Table I Comparison of the groups of baboons studied in the first hour after coronary artery ligation

	AC method		*DC method*		
	Survival	*VF*	*Survival*	*VF*	
No	*29*	*19*	*4*	*8*	*P value*
Body weight in kilograms	20 ± 0 9 o	21.2 ± 0 8 x	23 2 ± 1 7	24 5 ± 1.2 xo	x P < 0 0?5 o P < 0 0025
Sex	6F 23M	1F 18M	OF 4M	OF 8M	
Age	19A 10Y Oold	14A 4Y 1old	3A 1Y Oold	7A OY 1old	
Infarction size per cent total heart weight	*10 1* ± 0 5 o	*10 8* ± 0 8 x	7 6 ± 2 1	7 6 ± 1 1 xo	x P < 0 0?5 o P < 0 0?5
Approximate weight of infarction in grams	10	11	*9*	*9*	

Mean values ± S F M obtained from Student s t test
AC = alternating current DC = direct current F = female M = male Y = young adolescent (about 5 to 7 years) A = adult (about 8 to 20 years) Old = (about 20 to 30 years)

recorded at 1 mV = 1 mm and at 25 mm per second The time constant was 2 4 seconds and the frequency response between 0 4 to 40 Herz The input impedance was 2 mega ohms

The exploring epicardial electrode consisted of a flexible nylon insulated stainless steel wire One free end was bent in a narrow loop about 3 cm long and 2 mm wide The total weight resting on the heart was 0 1 gram The diameter of the wire was 0 3 mm The loop was closed by insulation wrapping and handheld for epicardial ECG recording at an angle of 180° with the epicardial surface The recording surface was calculated to be about 1 mm ² Wilson's central terminal was used as an indifferent electrode The heart was moistened with saline solution at 37° C before each epicardial ECG recording and was held gently during each recording to reduce the amplitude of heart movements and to facilitate and maintain heart surface electrode contact without interfering with the recording The epicardial electrode was moved over the left ventricle from the basis (A) next to the circumflex coronary artery toward the apex, and (B) back about 2 cm parallel to the anterior descending coronary artery (Fig 1) Another continuous recording was taken perpendicular to the previous one from the edge of the right ventricle (C) toward the edge of the left ventricle (D) and back and about 6 cm parallel to the atrioventricular groove The exploring electrode was not lifted from the heart during the path of movement during the period of each study which was about 20 to 30 seconds

Only animals with ST segment changes of less than +2 to −2 mV before coronary occlusion were retained in the experimental series The changes of the epicardial ST segment during the first minute of coronary occlusion were continuously recorded by the electrode held stationary in the anticipated center of the area progressively developing ischemia

The moving recordings were taken before coronary occlusion and at 15 30 and 60 minutes after ligation or until onset of ventricular fibrillation In 48 baboons the moving epicardial electrograms were recorded with the ac amplifier and stainless steel wire electrode moving at about 0 5 cm per second to 1 cm per second This recording speed resulted in minimal readjustment of base line shifts by the resistance capacitance coupling circuit (RC) during the continuous sweeping recordings However due to the existence of a RC circuit in all ac recordings some degree of damping of the ST segment changes recorded with the moving electrode had to be expected Therefore the epicardial ECG was recorded in another 12 baboons with a Tektronix memory oscilloscope Type 549 with a differential amplifier 1 A7A with a bandwidth adjusted from direct current (dc) to 1 KHz and an input impedance of 2 mega ohms A Beckman (mercury calomel 3 5 M KCl) electrode with a large porous glass membrane and attached cotton wick of 1 to 1 5 cm in length was used as an exploring electrode [11] A similar calomel wick electrode was used as a reference electrode and placed on a saline soaked cotton swab on the pubic bone of the animal Both electrodes were soaked in saline at 37° C before use The impedance of each electrode was measured and found to be 1 000 ohms for the



Baboon 105 A M 23 kg 10 / infarct

Before ligation

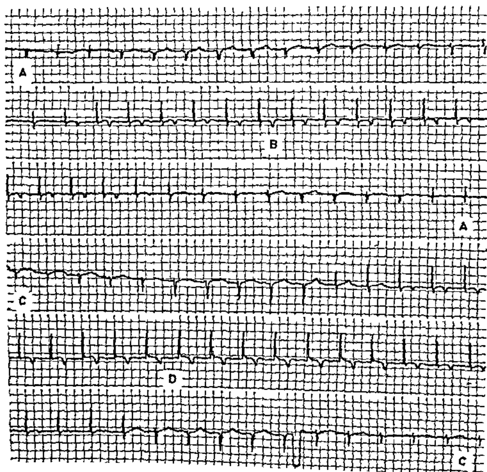


Fig 1 Continuous moving epicardial ECG recording in an adult male baboon of 23 kilograms. One solid square is 0 2 second by 5 mV Use of the wire electrode with ac method before ligation.

exploring electrode and 1 150 ohms for the reference electrode (measured from dc to 10 KHz) The half cell potential for each electrode was measured and found to be 300 millivolts with a differential of 1 7 mV between the electrodes when dipped in saline

The parameters measured were the maximal ST segment elevation and depression and the maximal baseline depression The latter was defined by the level of at least five consecutive TQ or TR segments of conducted sinus beats measured from the level of five consecutive TQ or TR segments of conducted sinus beats recorded in the control area as reference level The amplitude was measured from the baseline toward the middle of the ST segment or that part of the ST segment which was parallel with the baseline

Of the 60 animals studied 15 received no infusion after coronary artery ligation 16 received 0 5N NaCl infusion 11 received KCl and 18 received glucose insulin and potassium As

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	Survival	*VF*	*Survival*	*VF*	
No	*29*	*19*	*4*	*8*	*P value*
Body weight in kilograms	20 ± 0 9 o	21 2 ± 0 8 x	23 2 ± 1 7	24 5 ± 1 2 xo	x P < 0 025 o P < 0 005
Sex	6F 23M	1F 18M	0F 4M	0F 8M	
Age	19A 10Y 0old	14A 4Y 1old	3A 1Y 0old	7A 0Y 1old	
Infarction size per cent total heart weight	10 1 ± 0 5 o	10 8 ± 0 8 x	7 6 ± 2 1	7 6 ± 1 1 xo	x P < 0 025 o P < 0 005
Approximate weight of infarction in grams	10	11	9	9	

Mean values ± S E M obtained from Student's t test
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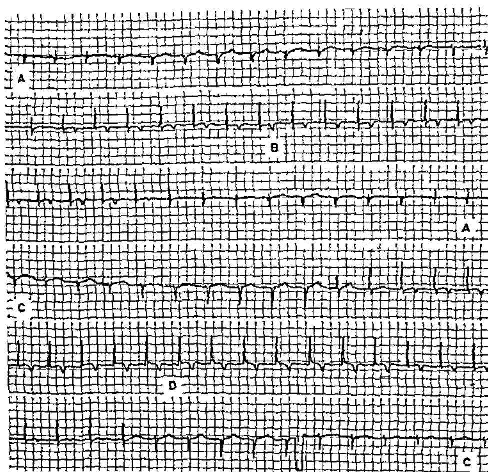


Fig 1 Continuous moving epicardial ECG recording in an adult male baboon of 23 kilograms One solid square is 0 2 second by 5 mV Use of the wire electrode with ac method before ligation

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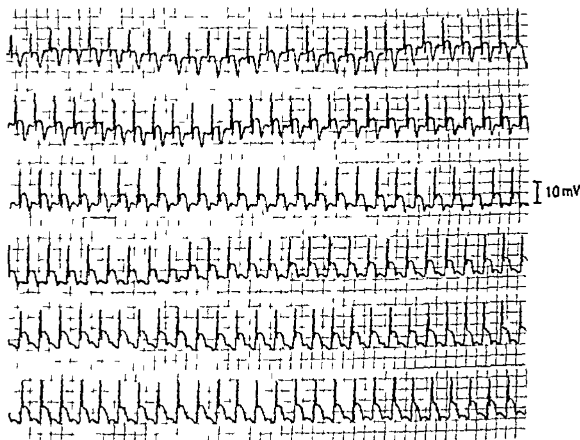


Fig 2 Continuous and stationary epicardial ECG recording in an adult male baboon of 23 kilograms from the center of the ischemic area during the first 60 seconds after total occlusion of the coronary artery with the wire electrode and ac method One solid square is 0 2 second by 5 mV

these infusions did not alter the degree of ST segment elevation in the infarction area[14] the results are grouped together except the values for ST segment depression in baboons infused with glucose insulin and potassium are omitted because such infusions decreased the rate of development of ST segment depression[14] Student s t test for unpaired or paired values was used to detect statistical significance Values are expressed as means ± S E M P values of less than 0 05 were regarded as significant

Results

The characteristics such as body weight sex age and size of the infarction of the 60 baboons used are given in Table I Twenty seven baboons developed spontaneously irreversible VF at an average time of 34 minutes after ligation No attempts were undertaken to convert ventricular fibrillation

The ac method with a wire electrode was used during the first experiments in which female baboons and young adolescent male baboons also were used This explains the lower average body weight in Table I in the groups where ac recordings were taken Although the percentage of the infarcted tissue in the ac groups is larger than in the dc group the total weight of infarcted tissue is similar for all groups A higher incidence of VF occurred during the series of experiments with dc recordings and wick electrode for no obvious reason except that females and young adolescent animals might more easily survive a standard size infarction than adult males[12]

ST segment changes in the first minute The anterior descending coronary artery was completely ligated after positioning the epicardial electrode in the anticipated center of the ischemic area of the ventricle A continuous stationary recording was made with the wire electrode and ac amplifier method in 41 baboons In all a progressive elevation of the ST segment developed within the first 60 seconds of occlusion The increase of ST segment was obvious after 20 to 30

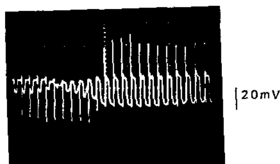


Fig 3 Continuous moving epicardial ECG recording in an adult male baboon of 21 kilograms from the edge of the right ventricle toward the edge of the left ventricle and through the infarction

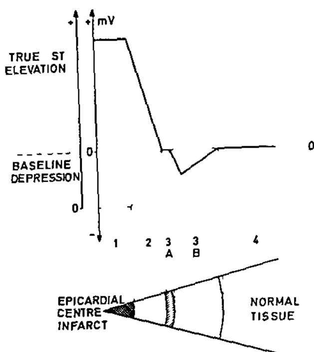


Fig 4 Schematic diagram of the five different epicardial ST segment areas in the presence of acute myocardial infarction in the baboon recorded with moving electrodes Area 1 center of infarction with maximal ST-elevation and depression of baseline Area 2 surrounding center of infarction with progressive decreasing ST elevation and diminishing baseline depression Area 3A narrow isoelectric band the danger area Area 3B with ST-depression with most depression nearest to the infarction Area 4 apparently normal tissue

seconds (Fig 2) The ST segment increased to an average of 6 4 to 8 mV respectively (values were not significantly different) in the groups which survived and which developed VF during the next hour A transient ST depression never did precede the development of ST elevation

Topography of ST segment changes A nearly constant pattern of ST segment changes was found during the epicardial sweeps The amplitude of ST segment changes was different from animal to animal and varied during the first hour However the two sweeping ECG recordings perpendicular to each other gave a fair idea of the areas with different ST segments Each epicardial sweep included its own control by the return movement closely following the path of the initial sweep (Figs 1 and 3)

The sweeping epicardial ECG traces after occlusion of the coronary artery showed the existence of five areas with different ST segment patterns (Fig 4) The color of the epicardial surface of the infarction areas one and two was blue brown with a sharply defined edge and bulging during systole Area one was the center of the infarction with maximal amplitude of isopotential ST segment elevation Such ST segment elevation was composed of the sum of a baseline depression and of an elevation of the ST segment (true ST segment elevation) measured from the level of the isoelectric baseline or consecutive TQ segments recorded in the control area four

Area two was a concentric area surrounding area one with a decreasing ST elevation amplitude and simultaneously decreasing baseline depression as the sweeping electrode moved from the infarction center toward normal tissue Area three A was a narrow belt like area surrounding area two with an isoelectric ST segment and apparently normal epicardial ECG Area three B was the area with epicardial ST segment depression surrounding area three A Area three A could only be demonstrated when a zone of ST segment depression (area three B) was present This was not always the case and when area three B existed it was not always concentric but sometimes limited to only part of the peri infarction zone

Area four was the apparently normal area with an isoelectric epicardial ST segment The blood flow and biochemical features of these zones have been defined elsewhere [14,15] When

Table II Comparison of ST segment changes in the first hour after coronary artery ligation

Minutes		*15*		*30*		*60*		*P value Student t test*
Method		*AC*	*DC*	*AC*	*DC*	*AC*	*DC*	
Maximal	Survival	16 5	30.2	18 3	23	22 3	27	x < 0 01
ST elevation		1 6	2 7	2.5	–	1 6	–	
		x (24)	(4)	(13)	(2)	x(29)	(2)	
	V F	18 9	25 1	17 6	26			
		2 3	3 3	2 5	7 1			
		(15)	(8)	(11)	(4)			
Maximal true	Survival	10 1	17 5	12 0	14 5	14 1	19	
ST elevation		1 2	2.3	2 0	–	1 1	–	
		x (24)	(4)	(13)	(2)	x (29)	(?)	x < 0 0[illegible]
	V F	12 5	8 4	13 3	16 7			
		1 5	2 5	2 0	2 9			o < 0 05
		(15)	(8)	(11)	(9)			
Maximal	Survival	6 0	11 7	6 3	9 0	8 4	8 5	x <0 025
baseline		x 0 8	2 3	1 2	–	x 0 9	–	
depression		(24)	(4)	(13)	(2)	(29)	(2)	
	V F	6 3	15 5	4 4	8 5			o<0 001
		1 3	2 2	0 8	5 0			
		(15)	(8)	(11)	(4)			
Maximal	Survival	2 9	3 5	3 6	5	4 8	4 5	x <0 05
ST depression		x 0 4	1 5	0 9	–	x 05	–	
without G I K		(14)	(4)	(9)	(2)	(10)	(2)	
	V F	3 7	3 6	3 9	1 0			
		0 6	1 3	1 0	1 0			
		(12)	(7)	(9)	(3)			
Ratio Maximum true ST elevation/	Survival	10 1 / 6 = 1 7	17 5 / 11 7 = 1 5	12 / 6 3 = 1 9	14 5 / 9 = 1 6	14 1 / 8 4 = 1 7	19 / 8 5 = 2 2	
Maximum base line depression	V F	12 5 / 6 3 = 2 0	8 4 / 15 5 = 0 5	13 3 / 4 4 = 3 0	16 7 / 8 5 = 2 0			

Results expressed in millivolts (mean values ± S E M)
Number of baboons in parentheses.

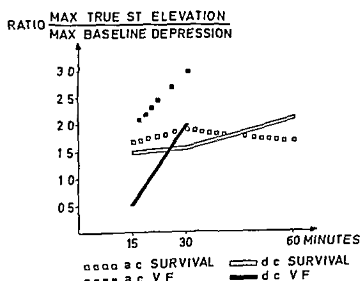


Fig 5 Change of the ratio maximal true ST elevation to maximal baseline depression during the first hour of coronary ligation in the groups which survived and the groups which developed VF

areas one, two, three A three B, and four were all present a complete pattern was deemed to be present The number of recordings with a complete pattern at 15 minutes were 42 of 51 baboons, and at 60 minutes 28 of 33 baboons

Maximal total ST elevation in area one The total ST segment elevation is the combination of true ST elevation and baseline depression Using the ac method the total ST elevation increased markedly from the first minute up to 15 minutes after ligation in the groups which survived the first hour and the group which developed VF but the values reached in the two groups at 15 and 30 minutes were similar (Table II) In the survival group there was a progressive increase of ST elevation between 15 and 60 minutes In the group developing VF ST segment elevation was unchanged at 15 and 30 minutes

Using the dc method and the wick calomel

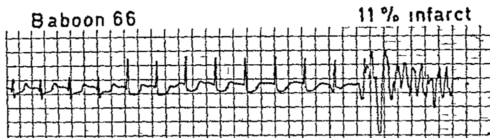


Fig 6 Continuous moving epicardial ECG recording with wire electrode and ac method from basis toward left ventricle apex When the electrode left the area with ST depression (area 3B) and crossed the area with isoelectric ST segment (area 3A) VF developed One solid square is 0 2 second by 5 mV., 66 minutes after ligation

electrode the ST segment elevation in area one was the same for the group which developed VF and the group which survived both at 15 and 30 minutes However the groups at 30 minutes were rather small

Maximal true ST elevation in area one The true ST elevation was the difference between the total ST elevation and isoelectric baseline in control area four There was an increase from 15 to 60 minutes in the group which survived when ac recordings were made In baboons who developed VF true ST elevation increased from 15 to 30 minutes with dc recordings True ST elevation remained unchanged in both other groups over the experimental period (Table II)

Maximal baseline depression in area one The maximal baseline depression never showed any difference between the group which developed VF and the group which survived at 15 or at 30 minutes with either recording system There was an increase of baseline depression in the group which survived when ac recordings were made between 15 and 60 minutes ($P < 0.02$ Table II) In contrast there was a progressive decrease in baseline depression between 15 and 30 minutes in the groups which developed VF This decrease was significant in the group developing VF recorded with the dc method ($P < 0.05$)

Maximal ST segment depression in area three B The values of maximal ST-depression never showed a significant difference between the baboons who developed VF and those who survived at 15 and 30 minutes after ligation with either the ac or dc method (Table II)) However the values of ST-depression in the group which survived with ac recording showed a significant increase between 15 and 60 minutes ($P < 0.05$)

Ratio Maximum true ST-elevation Maximum baseline depression This ratio was examined to determine possible changes in the relationship of the components of the total ST segment elevation The ratio remained nearly constant at 15 30 and 60 minutes in baboons who survived the first hour The ratio varied between 1 5 and 2 2 (Table II Fig 5) In contrast the same ratio tended to a rapid increase between 15 and 30 minutes in baboons who developed VF The ratio varied between 0 5 and 3

Provocation of dysrhythmias Ventricular ectopic beats were induced by the moving epicardial electrodes most frequently in the narrow border zone (area three A Fig 4) Ventricular fibrillation was induced in this area by the moving wire electrode in three baboons two of which were not included in the results while the third baboon (Fig 6) was included as a survival baboon to 60 minutes because VF was induced mechanically at 66 minutes Self limiting ventricular tachycardia was induced in this area in seven other baboons Thus of a total of 60 baboons 10 developed ventricular dysrhythmias by mechanical irritation of the border zone

Comparison of ac and dc methods The results and figures show that the two recording systems detect the same topographic phenomena of ST segment elevation ST segment depression baseline depression and pseudo isoelectric ST segment (area three A) when the recording epicardial electrode is moved continuously in and out of the infarction area The amplitude of ST elevation and depression of the baseline was higher with the dc method 15 minutes after ligation than the amplitude found with the ac method There was no difference for smaller amplitudes such as ST depression with both methods

Table II Comparison of ST segment changes in the first hour after coronary artery ligation

Minutes		*15*		*30*		*60*		*P value Student t test*
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	V F	18 9	2[illegible] 1	17 6	26			
		2 3	3 3	2 5	7 1			
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		1 3	2 2	°0 8	5 0			
		(15)	(8)	(11)	(4)			
Maximal	Survival	2 9	3 5	3 8	5	4 8	4 5	x < 0 0[illegible]
ST depression		x 0 4	1 5	0 9	–	x 0[illegible]	–	
without G I K		(14)	(4)	(9)	(2)	(10)	(2)	
	V F	3 7	3 6	3 9	1 0			
		0 6	1 3	1 0	1 0			
		(12)	(7)	(9)	(3)			
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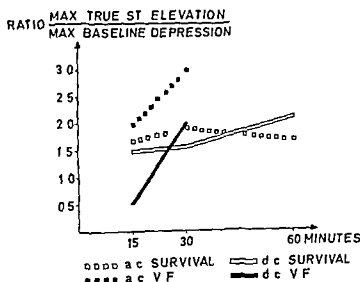


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Maximal total ST elevation in area one The total ST segment elevation is the combination of true ST elevation and baseline depression Using the ac method the total ST elevation increased markedly from the first minute up to 15 minutes after ligation in the groups which survived the first hour and the group which developed VF, but the values reached in the two groups at 15 and 30 minutes were similar (Table II) In the survival group there was a progressive increase of ST elevation between 15 and 60 minutes In the group developing VF ST segment elevation was unchanged at 15 and 30 minutes

Using the dc method and the wick calomel

their experiments and hence could not comment on whether ST changes could predict VF as they could predict the extent of necrosis Total ST elevation ST depression and baseline depression did not distinguish the group which survived from the group which developed VF using either ac or dc recording methods One exception consisted of the true ST elevation which was less 15 minutes after ligation in the group which subsequently developed VF than in the group which survived when recorded with the dc system

The maximal baseline depression became less with time in hearts prone to develop VF While total ST segment elevation did not distinguish the group of baboons which developed VF from the group which survived the first hour there were suggestive changes in the composition of total ST elevation These changes expressed as the ratio of maximum true ST elevation to maximum baseline depression developed especially quickly in the hearts which subsequently developed VF As precordial ST segment changes have been related to epicardial values [3] it may be that the fast changes in the components of precordial ST segment could be used to indicate imminent VF provided that true ST elevation and baseline depression could be separated

Samson and Scher[9] and Wallace[35] explained the baseline depression or TQ line by the diastolic electric current between the ischemic and healthy surrounding tissue The loss of baseline depression in the group which developed VF usually during the second half hour after coronary ligation could be due to an increasing inability of area one to be depolarized in the presence of severe metabolic gradients A short circuit is supposed to develop between the severely injured area one plus two and the less injured area three B with its maximal intensity in area three A An increased isolation of the injured cells with loss of intercellular bridges and progressive increase of resistance has been described to develop due to the healing over effect of the cells [36, 5] This effect probably develops most rapidly in the hearts prone to VF and could explain the rapid decrease of baseline depression or diastolic current

Limitations of methods

ac method The baseline depression due to a diastolic electric current between injured and non injured myocardium is a dc potential and when measured with a stationary electrode and the ac method it is not shown in the recording as such but noted as overall ST segment elevation With the ac method if the exploring electrode is moved from a normal area to an injured area baseline depression is measured but returns toward normal within 2 4 seconds the time constant of the ECG recorder used in these studies when the electrode is kept stationary For these reasons we moved the electrode smoothly and continuously at a speed of 0 5 to 1 cm per second between the points chosen on the ventricles Imperfect recordings often had to be repeated Half cell potentials develop when the exploring stainless steel wire electrode is brought in contact with the myocardium and the needle electrodes with the body tissue [40] The temperature of the surface of the heart and the electrode and local electrolyte concentrations influence the half cell potential development However half cell potentials develop only slowly after contact with body fluids A shift due to half cell potential was never recorded with the ac recorder independent of whether the electrode was sweeping or suddenly held stationary Moving in and out of the infarction area showed a clear change in the baseline It seems that the low frequency components generated by the half cell were outside the frequency response of the ac amplifier while the low frequency components of the base line depression in the ischemic area were within the low frequency range of the ac amplifier In addition the ac method with hot stylus direct writing recorder had a non linear amplification which dampened high amplitude ST segment signals

dc method No significant drifts were measurable Both the return to baseline and possible *baseline drift* were regularly checked by placing the exploring electrode on the saline soaked *cotton swab of the* reference electrode or by repetitive opening and closing of the circuit Minor drifts of the baseline in the range of 1 to 2 mV were recorded and could have been due to temperature changes such as heat from the hand holding the glass calomel electrode or by evaporation of moisture from the wet wick on the epicardium

A disadvantage of the calomel electrode with cotton wick of about 1 to 2 cm^2 was that its recording surface was 10 to 20 times the recording surface of the wire (1 mm^2) This larger recording surface could have resulted in an integral of different ST-segment values With both the wire and the cotton wick electrodes *moving* to and fro recordings at different times did not always

All epicardial sites recorded showed the same trend in ST segment changes during the first hour of observation after coronary artery ligation. The areas with maximal ST elevation and maximal baseline depression remained the areas of maximal ST changes throughout the experimental period. In no case did epicardial sites adjacent to each other but within the same zone (one, two, three B, or four, Fig. 4) show different or opposite ST segment changes. Therefore, we consider the changes found in areas one and three B with maximal ST segment deviations as representative for the direction of change of ST segment of the whole infarction during the first hour after coronary ligation.

Discussion

The existence of zones of lesion with different epicardial ST segment elevations within the infarction area resulting from coronary artery ligation and surrounding ST-segment depression have already been shown by Wolferth and Bellet[3] in 1945 and by Katcher, Pierce, and Sayen[4] in 1960. Our data obtained in baboons confirm these earlier findings in dogs. In addition, we describe apparently for the first time, a narrow border area with an apparently isoelectric ST segment. We have called this border area the "danger" area of the infarction because of the greater tendency of mechanical stimulation to cause ventricular dysrhythmias in this narrow zone. Han and co-workers[16-18] have stressed the concept of focal re-excitation and circus re-entry in the ischemic ventricle due to increased asynchrony of recovery at the boundary between the normal area and the ischemic area; they suggest an accelerated repolarization process. Antoni[19] suggested micro- and macro-re-entry pathways dependent on the conduction velocity and refractory period of adjacent fibers. The above observations should theoretically explain ventricular dysrhythmias due to re-entry with circuits not longer than 3 to 4 mm, no greater than the estimated size of the "danger zone." In 1956, Brofman, Leighninger, and Beck[20] found that dysrhythmias in experimental myocardial infarction arose in the zone between infarcted and non-infarcted myocardium. In 1962 Lushnikov[21] found a reduction of the dehydrogenase activity and a reduced number of formazan granules in the area at the edge of the infarction. Edwards[22] referred to the edge of the infarction as the "twilight zone" and Weissler[23] as the "zone of marginal perfusion."

In our baboon hearts, the infarctions were transmural as shown by large reduction of the coronary blood flow in the epi-, mid-, and endocardial regions.[13] There was an abrupt change from much reduced blood flow to the periphery of infarction zone (about 25 to 30 per cent of control) to immediately adjacent areas (three B, Fig. 4) where there was only a mild reduction of flow (70 per cent of control) in survival baboons, or even an increased blood flow in the baboons developing VF.[13] Thus, re-entry phenomena could develop due to the existence of extreme biochemical gradients between areas two and three-B (Fig. 4) as suggested by Dutta and Booker[24] and Bruyneel, Lubbe, and Opie.[25] However, the pathogenesis of dysrhythmias after myocardial infarction is complex and multifactorial. Hoffman and Cranefield[8] demonstrated that localized myocardial ischemia in a peri-infarction zone sensitized the adjacent automatic cells to the influence of catecholamines. Several authors[2, 31] have demonstrated the development of dysrhythmias caused by stretch (linear and concentric) of isolated muscle preparations or due to dilation or paradoxical movements of the ischemic muscles.

Although some of our groups are small, we have shown that ST-elevation, ST depression, and baseline depression did not reach a steady state 15 minutes after the infarction, but were still evolving up to 60 minutes after coronary artery ligation as demonstrated with the ac recording method. Maroko and co-workers,[6] studying dogs, also used an ac amplifier but found that the amplitude of ST segment elevation reached 15 minutes after ligation did not increase further thereafter.

A major difference between the data of Maroko and co-workers[6] and ourselves is that they used dogs and we used baboons. In the survival baboons, the mean rate of development of ST elevation was 6.4 mV at the first minute after occlusion, then about 0.7 mV per minute until 15 minutes, and then still a significant increase of 6 mV over the next 45 minutes (ac recordings, Table II).

In the dog, endocardial damage is greater than epicardial damage after coronary artery occlusion, whereas in the baboon flow reduction to epi-, mid-, and endocardial zones is equally severe[13] and there is greater depletion of ATP and of glycogen in epicardial than in endocardial infarction zones.[14] Maroko and co-workers[6] did not report on the incidence of dysrhythmias in

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follow the same track of a previous recording but instead followed a very similar path In practice it was shown that the recordings were highly repro ducible when taken shortly after each other

Conclusions

The above data demonstrate that the patterns of epicardial ST changes as recorded with a moving electrode after coronary artery ligation in the baboon yield similar information independent of the use of a wire electrode and an ac amplifier or a wick electrode and a dc amplifier The sweeping recordings delineated the existence of five different electrophysiologic epicardial areas and localized these areas quickly in comparison with static epicardial mapping A narrow area surrounding the infarction and with normal iso electric epicardial ST segment has been de scribed, apparently for the first time and called the danger area ' This area was more sensitive than other areas to mechanically induced dys rhythmias in agreement with some concepts of the site of origin of dysrhythmias in acute myocardial infarction

Absolute values of total ST segment elevation and depression true ST segment elevation, and baseline depression did not differentiate the animals which survived from the animals which developed VF throughout the first hour after coronary artery ligation ST segment changes developed quickly in the first 15 minutes and more slowly during the next 45 minutes and a steady state was not found during the first hour after coronary artery ligation This pattern of continuing evolution of ST segment over 60 minutes differs from that described for the dog

A rapid increase of the ratio maximum true ST elevation to the maximum baseline depression was found to precede the onset of VF If such a changing ratio were to have clinical value it could be of importance to separate and monitor the components of ST elevation during the first hours in patients with acute myocardial infarc tion Such advice would need reconsideration of the axiom put forward by Scher[11] in 1960 At present there seems to be no need to discriminate among these various causes (components) of ST segment elevation during acute and chronic occlusion of the vessels and such discrimination would present overwhelming technical prob lems'

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Table I Lack of correlation between the extension of cardiac infarction (per cent total left ventricular mass) and the degree of obstructive coronary damage

Per cent lumen reduction	No	< 49			50-69			> 70			Total
No of vessels	–	1 (%)	2 (%)	3 (%)	1 (%)	2 (%)	3 (%)	1 (%)	2 (%)	3 (%)	(%)
Infarction size (%)											
< 10	2 (7)	1 (3 5)	–	–	–	1 (3 5)	–	8 (2[illegible])	10 (34)	7 (24)	29 (100)
11-20	1 (5)	–	–	–	–	–	–	8 (40)	9 (45)	2 (10)	20 (100)
21-30	–	1 (4)	–	–	1 (4)	1 (4)	1 (4)	13 ([illegible])	6 (24)	2 (8)	25 (100)
31-40	1 (9)	–	1 (9)	–	–	–	–	3 (2[illegible])	5 (45)	1 (9)	11 (100)
41-50	–	–	–	–	–	–	–	6 (50)	5 (41)	1 (8)	12 (100)
> 50	–	–	–	–	–	–	–	1 (33)	1 (33)	1 (33)	3 (100)
Total	4	2	1	–	1	[illegible]	1	[illegible]3	36	14	100

obstructive arterioatherosclerotic coronary damage in individuals dying suddenly and unexpectedly and 100 hearts in subjects who died accidentally but who had lived under apparently healthy conditions were examined The control group was selected in a sex and age range similar to the previous groups

Results

Infarction cases In 100 cases with myocardial infarction (Table I) the size of the infarcted area ranged from less than 10 per cent to less than 60 per cent of the total left ventricular mass without correlation with the degree of obstructive coronary damage The following three patterns of myocardial necrosis were seen in the different zones

Coagulation necrosis This necrotic lesion—on which the pathologic diagnosis of myocardial infarction is based—is characterized by an early myocellular acidophilia nuclear changes and PMN infiltration which in the largest infarction stops along one well demarcated line occasionally associated with abscess like formations (Fig 1 *A*) The internal portion of the necrotic myocardium shows an elongation with reduction in the diameter of the muscle fibers and their nuclei The latter subsequently disappears (Fig 1 *B*) while the myofibrillar apparatus is still visible with an apparent increase in length of the sarcomeres The persistence of myofibrillar cross striations in register is documentable in the residual dead muscle fibers even in 25 day old infarction (Fig 1 *C*) The polymorphonuclear leukocytes undergo relatively rapid lysis and disappear within the first week No further infiltration by these elements occurs nor can fibrin deposition be detected Even in infarctions older than 10 days it is possible to demonstrate areas in which the infarcted tissue is adjacent to normal without any cellular infiltration at the junction (Fig 1 *D*) Furthermore the repair process which is variable in degree is carried out by macrophage activity and not by formation of granulation tissue (Fig 1 *E*) Finally the intramural vascular structures within the internal zone of the infarction undergo necrotic changes in their walls with secondary occlusive thrombosis In the external layer of the infarctions where hyperemia and PMN infiltration are prominent the muscle cell fibers generally show evidence of more or less extensive myofibrillar damage with irregular transverse band formations in the presence of an apparently normal nucleus (Fig 1 *F*) This histologic pattern is completely different from that just previously described in the internal portion of the infarcted myocardium

Coagulative myocytolysis In 13 (40 per cent) of 32 early infarctions (two days survival) there was histologic evidence of a different type of myocardial necrosis in the normal myocardium either at the border of the infarction or in the same region of the cardiac wall where the infarction was located Occasionally some of these foci were found in other normal cardiac regions Similar evidence was shown in 35 (92 per cent)of 38 acute infarction (ten days survival) and in 29 (96 per cent) of 30 recent cases who died within 25 days This type of necrosis appears to have a different evolution It seems to start with hypercontrac

Different types of myocardial necrosis in coronary heart disease A pathophysiologic review of their functional significance

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The basic irreversible lesion of the myocardium in acute 'coronary heart disease" (CHD) has been generally described as an ischemic coagulation necrosis of the muscle fibers with subsequent polymorphonuclear leukocytic (PMN) infiltration, granulation tissue, and scar formation[1, 2] It is a common experience, however, that a different morphologic type of myocardial cell death is frequently associated with the former[2-16] Schlesinger and Reiner[4] defined "myocytolysis as a selective, focal disappearance of the muscle cells without exudative or proliferative response They described these changes in 51 of 80 hearts with small and large recent infarctions, in 45 of 278 hearts with small and large myocardial fibrosis, and in 5 of 213 cases without myocardial damage This type of necrosis begins as a degenerative process involving primarily the myofibrils while the nucleus remains visible and apparently undamaged for some time The total disintegration of the myocardial cells results in a focus of empty, preserved sarcolemmal tubes associated with macrophages laden with a granular nonferrous yellow brown pigment The healing of these 'alveolar foci is accomplished by fibroblastic collagen condensation of the intact stroma without granulation tissue formation Finally, Saram[7] described a myofibrillar dissolution (fibrillolyse) secondary to a progressive intracellular edema at the edge of the infarction

The indiscriminate use of the term myocardial necrosis (frequently employed synonymously with infarction) and the resulting semantic confusion encouraged the present study on the possible functional significance of the different histologically demonstrable areas of myocardial necrosis in the natural history of CHD

Material and method

One hundred subjects who died following clinically documented myocardial infarction and found to have more or less extensive areas of coagulation necrosis of the myocardium with PMN infiltration were examined These patients died within 25 days from the onset of clinical symptomatology In order to investigate the chronology of the different morphologic variants the cases were divided according to their post attack survival time as follows (1) early infarction patients dying within two days (2) acute infarction death within 10 days and (3) recent infarction death within 25 days of the onset of clinical symptomatology The precise method for examination of the heart has been previously reported[17] In brief the heart was serially cross sectioned in 1 cm thick slices The area of each slice and the area of the infarction were measured by a polar planimeter and the percentage of necrotic tissue calculated with respect to the total ventricular mass From each cardiac section several samples were taken for histologic study at the center and from the border of the infarction as well as in the area of grossly normal myocardium The coronary arteries were examined by serial cross section at 3 mm intervals and the percentage of lumen reduction of each obstructive lesion was calculated by measuring with a micrometer the average diameter of the residual lumen and then relating it to the normal diameter of the vessel An average of 50 myocardial and coronary samples per heart were taken and stained by the hematoxylin and eosin phosphotungstic acid hematoxylin, and *Movat method*

Employing the same method 200 hearts with

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Fig 2 Different stages of extensive coagulative myocytolysis in normal myocardium around a human cardiac eight day old infarction The size of the infarction was 10 per cent of the left ventricular mass only *A* and *B* phosphotungstic acid hematoxylin ×440 Hypercontraction of muscle fibers alternated with segmental myofibrillar stretching and rhexis and early anomalous cross band formations The lesion at the intercalated disc level recalls the zonal lesion *C* hematoxylin and eosin × 620 Anomalous acidophilic cross bands associated with myofibrillar distension and breakdown No PMN infiltration shown *D* phosphotungstic acid hematoxylin ×160 Progressive disappearance of the alloplasmic material with mononuclear cell infiltration *E* hematoxylin and eosin ×550 Higher view Mononuclear cells and macrophages in empty spaces within myocardial cells showing anomalous cross bands *F* hematoxylin and eosin ×550 Empty intact sarcolemmal tubes resulting in the typical alveolar pattern

structure will progressively heal by fibroblastic collagenous fibril deposition resulting in a fibrous scar within which the pigmented macrophages can be seen In all different stages vessels of all types appear normal or dilated sometimes assuming a pseudoangiomatous aspect

Finally it must be noted that mononuclear cells lymphocytic in type may or may not be present in the coagulative myocytolytic foci When present they range from an occasional cell to an extensive infiltration No polymorphonuclear leukocytes are seen at any time

All different stages may be seen in the same involved zone but more frequently the same stage of necrosis is visible in various foci The extention and number of which varies in different

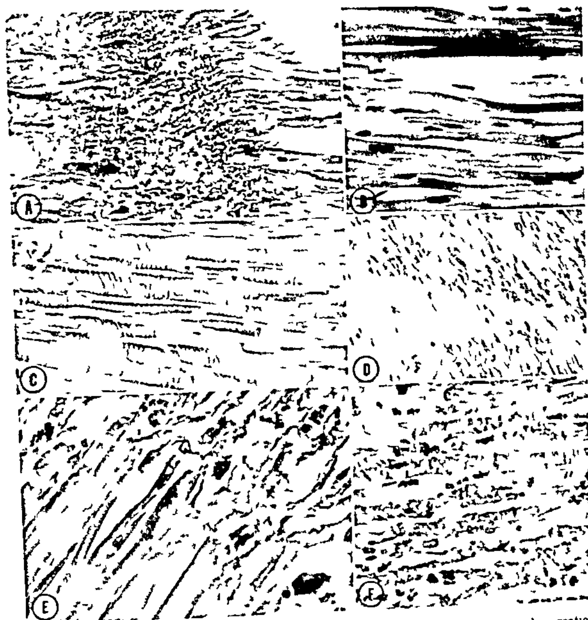


Fig 1 Different aspects of human cardiac infarction *A* hematoxylin and eosin ×160 Linear demarcation of the polymorphonuclear leukocytic infiltration with abscess like formation *B* hematoxylin and eosin × 450 Central part of an infarction Stretching of dead muscle fibers with elongation of the nuclei *C* hematoxylin and eosin ×450 Persistence of myofibrils with cross striations in registered order in a 25 day old myocardial infarction *D* hematoxylin and eosin ×160 Absence of reaction in a 10 day old myocardial infarction (upper site) *E* hematoxylin and eosin ×450 Absence of granulomatous tissue in the fibrotic repair process around the necrotic mass Note macrophages within the empty sarcolemmal tubes *F* hematoxylin and eosin ×450 Myofibrillar damage with anomalous transverse band formations in the external portion of a 24 hour old infarction with polymorphonuclear leukocytic infiltration

tion of the muscle fiber or a segment of it associated with stretching and breakdown of the myofibrils in the other segment of the cell or adjacent cells (Fig 2, *A* and *B*) This pattern is associated with abnormal, irregular transverse bands, variable in size and shape (Fig 2, *C*) which seem to be the result of a coagulation of hyper contracted sarcomeres This finding suggested the term coagulative myocytolysis' in defining this type of myocardial necrosis The damaged myocardial cells increase their affinity for acido philic stains The alternate pattern of rhexis and pyknosis of the myofibrils leads to a progressive disappearance of the contractile apparatus by macrophagic absorption producing an empty space within the single myocardial cell In the early phase, the nucleus is still visible appearing to be normal or at most, having an irregular deformed shape With the progression of the lytic process the whole nuclear alloplasmic complex disappears, leaving an empty intact sarcolemmal tube within which macrophages laden by gran ular yellow brown material are frequently seen (Fig 2 *D*, *E* and *F*) This 'alveolar residual

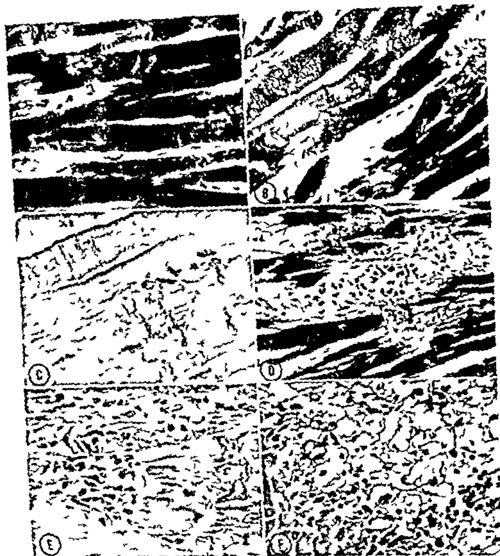


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All different stages may be seen in the same involved zone but more frequently the same stage of necrosis is visible in various foci The extention and number of which varies in different

Table II Lack of correlation between the degree of obstructive coronary damage and the occurrence of coagulative myocytolysis in 100 cases of acute cardiac infarctions

Per cent lumen reduction	*No*	*< 49*			*50 69*			*> 70*			
No of vessel	–	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*Total*
Total cases	4	2	1	–	1	2	1	39	36	14	100
Coagulative myocytolysis	4	2	1	–	1	1	1	37	35	14	96

Table III Lack of correlation between the presence or absence of coronary acute occlusion and the occurrence of coagulative myocytolysis

Infarcts	*Without acute occlusion*	*With occlusive thrombosis*	*Total*
Total	62	38	100
Coagulative myocytolysis	60	36	96

Table IV Lack of correlation between the size of infarction and the occurrence of coagulative myocytolysis

Infarction size (%)	*Total cases*	*Coagulative myocytolysis in*
< 10	29	28
11 20	20	20
21 30	25	24
31 40	11	11
41 50	12	10
> 50	3	3
Total	100	96

cases However, extensive confluent areas of coagulative myocytolysis, larger than the areas of coagulation necrosis can be observed

The different stages of this myocytolytic process do not correspond to the stages of coagulation necrosis Even in the older infarction it is possible to see foci of early coagulative myocytolysis This histologic pattern shown in the normal myocardium around the infarcted zone is similar to that previously seen in the external layer of the cardiac infarctions, the only difference being the presence of the PMN exudate in the latter If we include the earlier infarction cases the overall frequency of coagulative myocytolysis was 96 per cent

No correlation was found between degree of coronary arterio atherosclerosis number of vessels involved (Table II), presence or absence of an acute occlusion (Table III), size of the infarction (Table IV), and the occurrence of the coagulative myocytolysis

Colliquative myocytolysis This pattern of myocardial cell death may be defined as myocytolysis, colliquative in type, in contrast to the coagulative type described before In fact, instead of a breakdown and clumping of myofibrils in hypercontracted myocardial cells, dissolution of the myobrils appears to occur secondary to an edema like intracellular fluid with progressive vacuolization The result is again, an alveolar pattern formed by empty, dilated sarcolemmal tubes This type of necrosis occurs mainly as small foci in the subendocardial and perivascular muscle fibers which are generally preserved by coagulation necrosis (Fig 3 *A* and *F*) It was found in 31 2 per cent of the 32 early infarctions in 36 8 per cent of the 35 acute infarctions, and in 63 3 per cent of the 29 recent infarctions (overall frequency, 43 per cent) In the latter cases extension of the lesion was higher

Cases of sudden and unexpected coronary death Coagulation necrosis of the same range in size and histologic age as in the previous group was demonstrated in 16 per cent of these cases most of which (76 per cent) showed coagulative myocytolysis in the surrounding normal myocardium The latter however was the unique acute lesion found in 67 per cent of these cases In one subject very extensive coagulative myocytolysis (Fig 4, *A* and *B*) was associated with rupture of the heart and subsequent cardiac tamponade [19] A small focus of early coagulative myocytolysis associated with mild PMN infiltration was observed in 7 per cent of these instances Finally, in 10 per cent of the cases a focal colliquative myocytolysis located in the subendocardium was seen frequently in the presence of extensive myocardial fibrosis In Table V the pertinent main variants are given

Control cases Of 100 subjects dying by acci

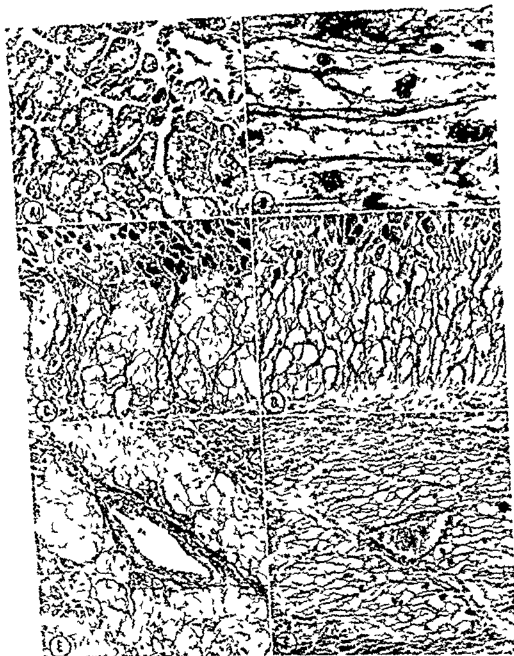


Fig 3 Colliquative myocytolysis in areas preserved by coagulation necrosis *A* and *B* hematoxylin and eosin, ×540 Progressive intracellular edema with vacuolization in transverse (*A*) and longitudinal (*B*) view Persistence of an apparently normal nucleus in transparent myocells with *myofibrillar dissolution C* and *D* hematoxylin and eosin ×180 Progressive subendocardial colliquative *myocytolysis ending in* empty sarcolemmal tubes *E* periodic acid Schiff ×180 Preserved myocardium in a perivascular zone *F* hematoxylin and eosin ×180 Zone in an area of early coagulation necrosis (*E*) *compared with a similar* zone which has undergone colliquative myocytolysis (*F*)

dent 27 cases showed very small and rare foci of coagulative myocytolysis In six instances the pattern was alveolar in type while in the other 21 an occasional single myocardial cell or a group of a few myocardial cells showed myofibrillar rhexis and anomalous bands Out of these 27 cases 17 had normal coronary arteries and 10 had severe obstructive arterio atherosclerotic lesions of the main subepicardial branches of the coronary arteries In no instance was coagulation necrosis or colliquative myocytolysis observed

In all the groups examined no relation between

Table II Lack of correlation between the degree of obstructive coronary damage and the occurrence of coagulative myocytolysis in 100 cases of acute cardiac infarctions

Per cent lumen reduction	*No*	*< 49*			*50 69*			*> 70*			
No of vessels	–	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*Total*
Total cases	4	2	1	–	1	2	1	39	36	14	100
Coagulative myocytolysis	4	2	1	–	1	1	1	37	35	14	96

Table III Lack of correlation between the presence or absence of coronary acute occlusion and the occurrence of coagulative myocytolysis

Infarcts	*Without acute occlusion*	*With occlusive thrombosis*	*Total*
Total	62	38	100
Coagulative myocytolysis	60	36	96

Table IV Lack of correlation between the size of infarction and the occurrence of coagulative myocytolysis

Infarction size (%)	*Total cases*	*Coagulative myocytolysis in*
< 10	29	28
11 20	20	20
21 30	25	24
31-40	11	11
41 50	12	10
> 50	3	3
Total	100	96

cases However, extensive confluent areas of coagulative myocytolysis larger than the areas of coagulation necrosis can be observed

The different stages of this myocytolytic process do not correspond to the stages of coagulation necrosis Even in the older infarction it is possible to see foci of early coagulative myocytolysis This histologic pattern shown in the normal *myocardium around the infarcted zone is similar* to that previously seen in the external layer of the cardiac infarctions, the only difference being the presence of the PMN exudate in the latter If we include the earlier infarction cases the overall *frequency* of coagulative myocytolysis was 96 per cent

No correlation was found between degree of coronary arterio atherosclerosis number of vessels involved (Table II), presence or absence of an acute occlusion (Table III), size of the infarction (Table IV), and the occurrence of the coagulative myocytolysis

'Colliquative myocytolysis This pattern of myocardial cell death may be defined as myocytolysis colliquative in type in contrast to the coagulative type described before In fact, instead of a breakdown and clumping of myofibrils in hypercontracted myocardial cells dissolution of the myobrils appears to occur secondary to an edema like intracellular fluid with progressive vacuolization The result is again, an alveolar pattern formed by empty, dilated, sarcolemmal tubes This type of necrosis occurs mainly as small foci in the subendocardial and perivascular muscle fibers which are generally preserved by coagulation necrosis (Fig 3 *A* and *F*) It was found in 31 2 per cent of the 32 early infarctions, in 36 8 per cent of the 35 acute infarctions, and in 63 3 per cent of the 29 recent infarctions (overall frequency, 43 per cent) In the latter cases extension of the lesion was higher

Cases of sudden and unexpected coronary death Coagulation necrosis of the same range in size and histologic' age as in the previous group was demonstrated in 16 per cent of these cases most of which (76 per cent) showed coagulative myocytolysis in the surrounding normal myocardium The latter however, was the unique acute lesion found in 67 per cent of these cases In one subject very extensive coagulative myocytolysis (Fig 4 *A* and *B*) was associated with rupture of the heart and subsequent cardiac tamponade [13] A small focus of early coagulative myocytolysis associated with mild PMN infiltration was observed in 7 per cent of these instances Finally in 10 per cent of the cases a focal colliquative myocytolysis located in the subendocardium was seen frequently in the presence of extensive myocardial fibrosis In Table V the pertinent main variants are given

Control cases Of 100 subjects dying by acci

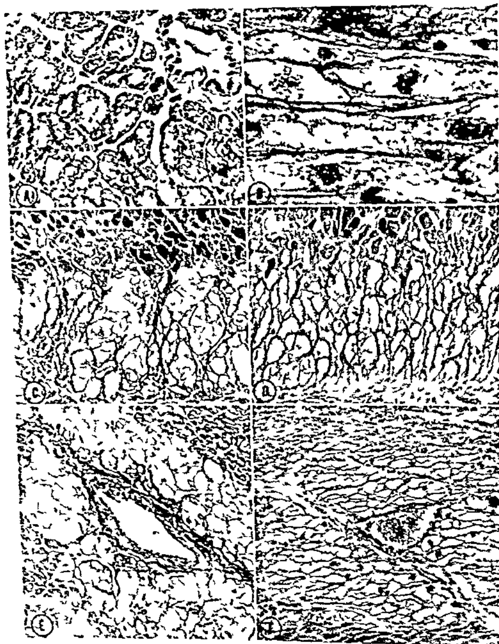


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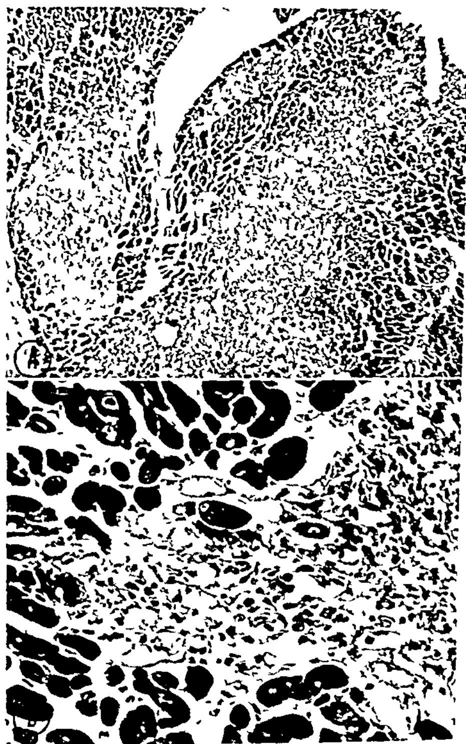


Fig 4 Coagulative myocytolysis in sudden coronary death A phosphotungstic acid hematoxylin ×80 B phosphotungstic acid hematoxylin ×220

age and sex and the incidence of the two types of myocytolysis was detected

Discussion

Many uncertainties still exist in understanding the pathogenesis of CHD[17,20] limiting us to a definition based only on morphologic features However, the finding of distinctive types of myocardial necrosis in CHD cases (showing a clear cut histologic difference in their earlier stages) leads one to assume a diverse mechanism for the functional death of the myocardial cell This, in turn suggests a different pathogenesis with different biochemical derangements In coagulation necrosis in which the earliest changes involve the mitochondria and the nucleus with PMN infiltration but without evident damage of the myofibrillar system [an observation already emphasized in both human[2,12] and experimental infarction[9,11]] the initial impairment is a loss of

Table V Percentage distribution of coronary and acute myocardial damage in 200 cases of sudden *coronary death

Per cent lumen reduction	< 49				50 69				> 70			
No of vessels	*1*	*2*	*3*	*Total*	*1*	*2*	*3*	*Total*	*1*	*2*	*3*	*Total*
Total (%)	23 5	41 1	35 2	8 1	36.3	45 4	18 1	10 5	31 8	37 5	30 5	75 4
Acute occlusive thrombus	–	–	–	–	100	–	–	0 4	90 4	9 5	–	10 0
Coagulation necrosis	100	–	–	0 4	–	100	–	0 4	34 3	43 7	21 8	15 3
Myocytolysis coagulative	33 3	40 0	26 6	7 2	38 4	46 1	15 3	6 ?	23 6	40 0	36 3	52.8
Myocytolysis colliquative	–	–	–	–	–	100	–	0.5	6 6	40 0	53 3	8 1

contractility possibly due to intracellular acidosis and consequent calcium pump deficiency in promoting contraction[2] The myocardial cell dies in an atonic state with passive overdistention due to the intraventricular pressure and the systolic bulging The consequent increase in interstitial tissue pressure and the subsequent vascular thrombosis within the necrotic area further aggravate the reduction of the intramural flow which is already minimal at the beginning in the central zone [1] starting an ischemic vicious circle The contour line where the PMN infiltration stops could be the morphologic sign of blockage of flow around the noncontracting area The opposite pattern is seen in the coagulative myocytolysis In this type of myocardial necrosis the myocell dies in a hypercontracted state (tetanic death) with myofibrillar rhexis and anomalous cross band formation but without nuclear changes PMN infiltration and vascular damage This myofibrillar lesion is defined as myofibrillar degeneration"[2] or when limited to the intercalated disc region as a zonal lesion [5] and is often referred to as contraction band, appears to be the early stage of coagulative myocytolysis as shown by the pre ence in the same case of various stages (from the myofibrillar damage in hypercontracted muscle fibers to the healing of the alveolar foci formed by empty sarcolemmal sheaths) The myocardium in cases of pheochromocytoma [2] and in experimental catecholamine induced necrosis [*] in which the coagulative myocytolysis is the characteristic type of myocardial necrosis found are strongly suggestive for a possible primary role of the catecholamines in the pathogenesis of the coagulative myocytolysis In fact a sympathetic over stimulation may determine an irreversible contractile state with myofibrillar damage by a massive increase in transmembranous Ca influx with depletion of high energy phosphates [3] [33] A more complex dysionism [3] however in which the role of other ions [2] [3] [37] and hormones have to be considered [3] Finally the myocardial cell may die in a failing state with progressive intracellular edema and vacuolization and in which the main early finding is an edema with dissolution of the myofibrils (colliquative myocytolysis) without other changes peculiar to the other two types of necrosis a pattern usually found in the alcoholic cardiomyopathy with low output syndrome [31]

Using this morphologic background one is tempted to speculate the following possibilities in the natural history of CHD In the cardiac infarction namely coagulation necrosis the negative hemodynamic effects due to the loss of contractility can only be balanced by the hyperfunction of the viable myocardium especially at the borderline of the noncontracting region Hyperfunction of the normal myocardium has been demonstrated likely mediated by catecholamines [*] which are in general increased in the serum of patients with an infarction [34] [1] [2] This could explain the coagulative myocytolysis both in the outer zone of the acute infarction (and therefore associated with PMN infiltration elicited by the coagulation necrosis itself) and in the normal myocardium adjacent to an infarction at any stage of its repair process a damage similar to that found in experimental acute aortic stenosis with acute ventricular hyperfunction [3] [1] However the very high frequency of co

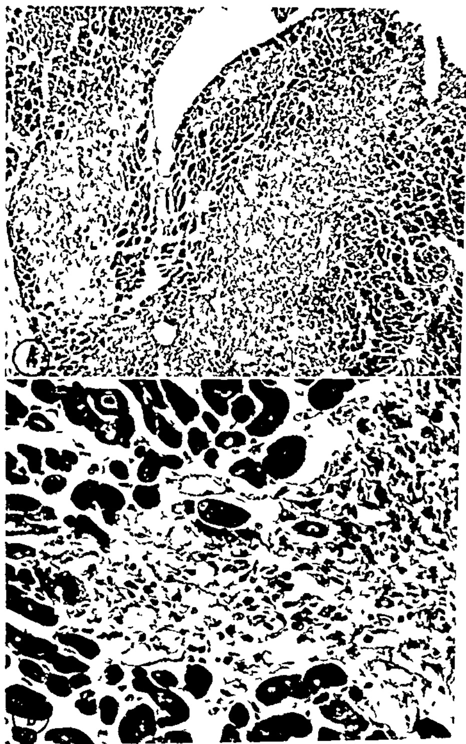


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agulative myocytolysis as a unique acute necrotic lesion in cases of sudden "coronary" death and the cases with small sized coagulation necrosis associated with extensive coagulative myocytolysis, supports the concept of a possible primary sympathetic stimulation likely due to various congenital and acquired factors Obviously, in the sudden death cases, we cannot exclude the association with an early coagulation necrosis, undetectable by histologic methods It must be stressed that both coagulation necrosis and coagulative myocytolysis show early acidophilic changes We do not know the difference if any in the enzymes lost Therefore, the methods for the early detection of an infarction seem inadequate or at least questionable in differentiating these two types of necrosis However the fact that cases of sudden death show only coagulative myocytolysis in different stages of the repair process strongly suggests that a primary catecholamine like death may have occurred For example, CHD cases with cardiac arrest, successfully treated by defibrillation without further evidence of an infarction [44] seem to support this view

Therefore, the coagulative myocytolysis even if limited to a few myocells seems to be a very important histologic landmark linked with a complex functional biochemical disorder in turn associated with a fatal ventricular fibrillation The relation between the latter and the catecholamines has been stressed [45, 46] On the other hand ventricular fibrillation appears to be the most common immediate cause of death in CHD while other causes such as the failure of the cardiac pump (as shown by the colliquative myocytolysis as a consequence of progressive stasis with persistent washout effect and intracellular colliquation in muscle fibers located at the blood front) or rupture of the cardiac wall at the site of coagulation necrosis, etc seem to have a lesser incidence

In conclusion, from the present data, it seems essential to recognize the different types of the myocardial cell death because of their possible assistance in defining the experimental and human cardiomyopathies in general and *CHD* in particular For instance the present study suggests that the reduction or the increase in size of an infarction[47-50] is due more to the change in extension of the secondary coagulative myocytolysis than to a change in size of the primary coagulation necrosis Therefore the understanding of the natural history and the pathogenesis of the CHD requires an understanding of the natural histories and the pathogeneses of all different types of myocardial necrosis, all of which are, at present of controversial origin In human coagulation necrosis, there is no morphologic proof that the cause is an acute coronary occlusion The role of ischemia is also debatable [11, 51] The same uncertainty exists in interpreting the underlying mechanism in the cardiac failure and catecholamine induced necrosis In the latter, spasm,[5] platelet aggregation [53] steal syndrome [54] occlusion of the penetrating branches because of the displacement of the two major cardiac muscle coats after prolonged ventricular fibrillation,[45] have been suggested However, no histologic sign of vascular impairment was shown in our material and no flow reduction has been demonstrated in this type of necrosis [5]

From the present data the coagulative myocytolysis (as a sign of a severe biochemical impairment resulting in ventricular fibrillation) appears to be the main cause of death in CHD, a cause which, at present, seems more a *metabolic* problem than a vascular one The theoretical and therapeutic implications are obvious

Summary

The different histologic types of myocardial necrosis have been investigated in 100 acute cardiac infarctions in 200 sudden coronary deaths, and in 100 control cases The incidence as well as the frequent association of three different morphologic patterns of myocardial necrosis suggest that various pathogenetic mechanisms with different biochemical derangements may interact in the natural history of the coronary heart disease

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Packed cells platelet-rich plasma and adenosine diphosphate in the production of occlusive vascular changes in lungs of rabbits

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Although in many cases pulmonary hypertension is secondary to the associated cardiac or lung diseases there is at times pulmonary hypertension for which no etiologic factor can be incriminated This group is termed as primary pulmonary hypertension Two major hypotheses have been put forward to explain the occurrence of this condition (1) recurrent thromboembolism in the pulmonary circulation and (2) prolonged vaso spasm It is difficult to prove these hypotheses in human patients but experiments are being designed in which these two factors can be tested Fibrin embolism and autologous blood clots have been injected into the pulmonary circulation and vascular changes suggestive of hypertension have been produced in experimental animals[1,2,3] McLetchie produced thrombosis in the pulmo nary arteries by intravenous injection of throm boplastin which ultimately caused diffuse arterio sclerosis but he did not study hypertension in these cases Nityanand Zaidi Chakravarti[5] and Nityanand and Zaidi[6] demonstrated the marked aggravating effects of adrenaline and serotonin on pulmonary arteriosclerosis produced by fibrin embolism in rabbits Contrary to the role of particulate components of blood causing this condition Merida and Reeves demonstrated that hemolyzed blood could also cause pulmonary vascular changes suggestive of hypertension in rabbits In this laboratory Kottor Wahi and Chakravarti observed that injection of autolo gous hemolyzed blood caused eccentric intimal thickening in medium and small arteries with a variable degree of medial hypertrophy The present experiment was designed to study the role of individual blood components including packed cells (three per cent suspension of homologous erythrocytes in physiologic saline) platelet rich plasma and a solution of adenosine diphosphate (ADP) which is released on platelet disintegra tion This study was thought to give further insight into the pathogenesis of primary pulmo nary hypertension

Material and methods

Adult healthy rabbits with a body weight of 1 5 to 2 kilograms were employed The stock diet given to these animals consisted of soaked bengal gram with bran and green grass Water was given and libitum There were five groups each having six animals

Group I In this group the animals were subjected to biweekly intravenous injection of packed cells (three per cent v/v homologous washed erythrocytes suspended in physiologic saline) extending over a period of three months (Table I)

Group II These animals received homologous plasma rich in platelets intravenously twice a week over a period of three months (Table I) For the preparation of platelet rich plasma blood was collected from the marginal ear vein in a heparin ized syringe and the blood centrifuged in a poly ethylene tube at 1 000 r p m for ten minutes The plasma was separated by means of a pipette That

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Fig 2 Section of lung of animal in Group I (packed cell) at 12 weeks showing marked vasospasm of pulmonary artery Hematoxylin and eosin ×100



Fig 3 Section of lung of animal in Group II (platelet rich plasma) at 12 weeks showing marked degree of medial hypertrophy of small and medium sized pulmonary arteries There is vasospasm also causing severe narrowing of the lumen Hematoxylin and eosin × 100

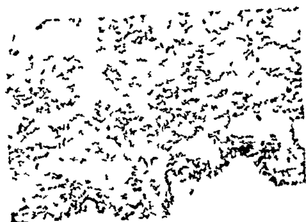


Fig 4 Section of lung of animal in Group II (platelet rich plasma) at 12 weeks showing a fully organized and recanalized pulmonary artery thrombus Hematoxylin and eosin ×100



Fig 5 Section of lung of animal in Group IV (ADP) at 12 weeks showing marked intimal hyperplasia with elastosis in a large pulmonary artery Aldehyde fuchsin ×100

mentioned above were assessed by actual measurement under a microscope using an ocular micrometer Statistical analysis of the data was made The arteries were classified according to their size into three categories viz 0 to 150 μ 151 to 300 μ, and above 301 μ

Results

Following intravenous injection of various blood components no shock or symptoms suggestive of respiratory distress were noticed in the animals However the electrocardiogram showed evidence of right ventricular dominance in animals belonging to Groups I II and IV and in few animals right atrial hypertrophy was present at the six week period (Fig 1)

Histopathologic findings Abnormal structural changes in the pulmonary vasculature was noted in Groups I II and IV i e animals receiving packed cells plasma rich in platelets and ADP solution The animals of Group I showed evidence of medial hypertrophy in small and medium sized arteries the mean value ± S D being 18 4 ± 5 9 as against 7 3 ± 2 7 and 33 1 ± 9 9 as against 9 3 ± 2 6 μ in the control (Group V) This was statistically significant ($p < 0.01$) In two animals fibrous intimal thickening in large pulmonary arteries were noted In medium and smaller vessels vasospasm of moderate degree was seen (Fig 2)

In Group II animals which received plasma rich in platelets one animal died after three weeks of injections in which no evidence of infection could be seen in the lungs Examination of

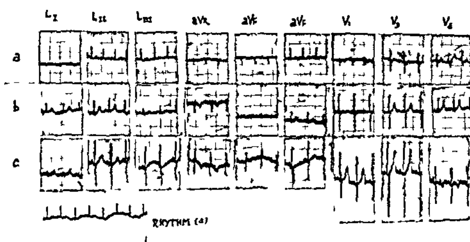


Fig 1 The electrocardiogram of an animal in Group II (platelet rich plasma) at (a) zero hour (b) 6 weeks and (c) 12 weeks There is marked change in axis at 6 and 12 weeks and atrial and right ventricular dominance Heart rate slowed down from 250 to 187 per minute

Table I

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
	3 per cent packed cells in normal saline	*Plasma rich in platelets*	*Plasma without platelets*	*ADP (2 μg/ml)*	*Normal saline*
No of rabbits	*Doses (ml)*	*Doses (ml)*	*Doses (ml)*	*Doses (ml)*	*Doses (ml)*
1 2	2	2	2	2	2
3 4	4	4	4	4	4
5 6	6	6	6	6	6

this plasma contained platelets in large number was confirmed by examining stained smears

Group III In this group, plasma was centrifuged at a high speed of 3,500 r p m for 20 minutes to free it from platelets and then it was injected intravenously as above (Table I) Smears made from the plasma did not show any platelets

Group IV In this group, animals received intravenous injections of a freshly prepared solution of adenosine diphosphate (trisodium salt Fluka) in a strength of 2 μg per millilıter The injection schedule was the same as above (Table I)

Group V This group served as control where isotonic saline was given intravenously

All these animals received injections of intramuscular soluble penicillin 5,000 units, and streptomycin, 50 mg, twice weekly to prevent any pulmonary infection Apart from studying the general condition and food intake of the animals throughout the experiment, electrocardiograms were recorded at the start, in the middle of the experiment, and preterminally The leads used were I, II III aV_R, aV_L aV_F and chest Leads V_1 V_3 and V_6 At the end of the experiments the animals were killed and an autopsy was performed Both lungs and heart were examined in situ and then dissected out Any evidence of hemorrhage infarction or other lesion was noted Tissues were fixed in four per cent neutral formaldehyde solution after inflation

One block was cut transversely from each lobe of the lungs and paraffin sections of 5 μ thickness were stained with hematoxylin and eosin, Mallory s PTAH, alcian blue PAS, and Verhoeff's iron hematoxylin The pulmonary arteries were examined for evidence of intimal thickening medial hypertrophy, lumen occlusion periarteritis and other lesions suggestive of pulmonary hypertension At identical sites in each lung changes

Intimal thickness (microns)		
0 150	*151 300*	*301 above*
Nil	6 22 ± 3 9 P < 0 01	15 6 ± 4 5 P < 0 01
Nil	13 8 ± 10 2 P < 0 01	28 8 ± 20 0 P < 0 01
Nil	Nil	Nil
Nil	9 2 ± 8 2 P < 0 02	27 0 ± 12 2 P < 0 01
Nil	Nil	Nil

substantiate the existence of pulmonary hypertension yet the electrocardiographic findings of right ventricular dominance in animals given packed cells platelet rich plasma and ADP solution did suggest this possibility

The common pathologic features observed in the animals given packed cells platelet rich plasma and ADP solution were diffuse medial hypertrophy in arteries of small and medium size vasospasm eccentric intimal hyperplasia usually in medium and larger arteries and thrombosis causing partial or complete occlusion of the vascular lumen Evidence of mild arteritis was also seen in a sizable number of animals These pathologic changes are well known to occur in cases of pulmonary hypertension and could be placed in Grade III and IV of Heath and Edward s classification Very advanced lesions of pulmonary hypertension were not seen in these animals because of the short duration of the experiments It appears that the rabbit can be used as an experimental animal for the study of the pathogenesis of primary pulmonary hypertension Earlier in this laboratory Kottor Wahi and Chakravarti had shown in rhesus monkeys that prolonged injection of autologous hemolyzed blood could induce medial hypertrophy and intimal hyperplasia in medium and large pulmonary arteries They suggested that these lesions could be the end result of multiple recurrent mural thrombi In the light of these observations it seems pertinent to postulate that blood components play a significant role in the production of primary pulmonary hypertension

The exact mechanism of the changes produced in the pulmonary vasculature following injections of packed cells, platelet rich plasma and ADP solution is not clear However it is known that platelets are a rich source of certain amines including 5 HT (serotonin) histamine as well as adrenaline and noradrenaline[1] These are known vasculotoxic and thrombogenic agents Erythrocytes and platelets are known to contain ADP[11] which when released into the circulation as a result of breakdown of these cells promotes thrombosis by causing platelet aggregation[11] It is therefore possible that the disintegration of cellular components could have released some of these substances which were responsible for the pulmonary vascular pathology observed That ADP plays a significant role in causing pulmonary vaso occlusive pathology has also been shown in this experiment

Summary

An experimental study to simulate the lesions of primary pulmonary hypertension was undertaken in rabbits Five groups were made each having six animals and these were given separately packed cells (3 per cent suspension of homologous erythrocytes in physiologic saline) plasma rich in platelets plasma without platelets ADP solution and normal saline injections biweekly for a period of three months Clinical electrocardiographic and histologic examination of the lungs were made It was noted that animals given packed cells plasma rich in platelets and ADP solution developed electrocardiographic changes and histologic lesions in the lungs suggestive of pulmonary hypertension

The authors are thankful to Shri H S Komal for technical help Shri G S Sekhon for executing the photomicrographs and Shri Harjindar Singh Kamboj for typing the manuscript

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Table II

	External diameter (microns)			*Internal diameter (microns)*			*Medial thickness (microns)*		
	0 150	*151 300*	*301 above*	*0 150*	*151 300*	*301 above*	*0 150*	*151 300*	*301 above*
Group I 3 per cent packed cells	100 6 ± 26 5	190 7 ± 32 7	327 2 ± 37 2	59 8 ± 29.2 N S	124 8 ± 29 2 P < 0 05	203 6 ± 52 7 N S	18 4 ± 5 9 P < 0 01	33 1 ± 9 9 P < 0 01	56 3 ± 16.1 N S
Group II platelet rich plasma	97 3 ± 33 7	208 7 ± 44 5	453 2 ± 148 8	58 1 ± 21 8 N S	134 2 ± 34 6 N.S	290 9 ± 94 5 N S	21 3 ± 7 4 P < 0 01	36 3 ± 11 5 P < 0 01	73 3 ± 17.2 N.S
Group III plasma without platelets	84 7 ± 22 0	178 1 ± 21 4	Nil —	70 0 ± 23 0 N S	158 3 ± 21 5 N S	—	7 1 ± 1 7 N.S	9 8 ± 2 5 N S	Nil
Group IV ADP	92 6 ± 25 5	212 6 ± 38 9	459 9 ± 123 9	58 9 ± 22 1 N S	147 5 ± 34 4 N S	341 7 ± 88 7 P < 0 05	17 5 ± 4 7 P < 0 01	30 8 ± 1 1 P < 0 01	49 1 ± 14 8 N S
Group V normal saline control	82 0 ± 23 1	178 8 ± 22 7	354 9 ± 52 3	66 6 ± 21 6	160 2 ± 20 4	226 2 ± 99 2	7.3 ± 2 7	9 3 ± 2 6	64.3 ± 44 7

Comparison has been made between control and treated groups for statistical evaluation of data
N S Not significant



Fig 6 Section of lung of animal in Group IV (ADP) at 12 weeks showing freshly formed and organizing mural thrombus in a large pulmonary artery Hematoxylin and eosin ×100

the lungs of the remaining animals which were killed at the end of the experiments showed diffuse lesions in the pulmonary arteries characterized by medial hypertrophy intimal hyperplasia, elastosis, and thrombosis In arteries of all sizes the medial thickness was greater as compared to the control value but a highly significant difference was noted when arteries with an external diameter less than 300 μ were considered ($p < 0\ 01$) and Fig 3 Intimal hyperplasia was significant in medium and large arteries (Table II) Some of the thrombi were in the process of organization and in one medium sized artery, a fully organized and recanalized thrombus was noted (Fig 4) Marked vasospasm was also noted in these vessels

In Group IV animals which received ADP solution diffuse medial hypertrophy of moderate to severe degree in medium sized and small arteries and in arterioles was detected The mean values of this parameter in small and medium sized arteries were 17 5 ± 4 7 and 30 8 ± 9 1 μ which were significantly greater than the control values ($p < 0\ 01$) Some degree of intimal hyperplasia with elastosis was noted in medium and large arteries (Fig 5 and Table II) In addition mural thrombi were seen in many arteries (Fig 6) Mild arteritis and marked vasospasm were also noted In the remaining two groups i e III and V, the animals did not present any pathologic feature on microscopic examination of lungs

Discussion

The present experiments have provided evidence that introduction of certain individual blood components into the pulmonary circulation can give rise to changes in the arteries and arterioles of the lungs suggestive of pulmonary hypertension Although pressure studies could not be undertaken in these experiments to

A new method for automated detection of the R on-T phenomenon

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Continuous automatic monitoring of rhythm disturbances is possible bv use of analog computers capable of on line detection of ectopic beats [1,2] Ectopic beats interrupting the T wave of the antecedent beat (R on T phenomenon) are often precursors of ventricular fibrillation in patients with myocardial infarction [5,10] Today s methods for automated detection of the R on T phenomenon are either too complicated or lack reliability Therefore a new simple method was developed based on the continuous evaluation of the QT time which is then compared to the RR distance of each beat

Method

According to Lown and co workers [1] and Buechner and Effert [3] the degree of prematurity of an ectopic beat can easily be described by the following quotient

$$\frac{R_{ES} - Q_N}{T_N - Q_N}$$

In the method presented here (Figs 1 and 2 for a more detailed description see Reference 4) the coupling interval (R_{ES} Q_N) and the QT time (T_N Q_N) are evaluated and then compared to each other The analog circuit works as follows The RR interval is determined on a beat to beat basis by measuring the interval between two trigger signals (Fig 2, signal 3 2) corresponding to the onset of each QRS complex These QRS signals are used to control an integrator forming ramp pulses the maximum of which is proportional to the coupling interval Each ramp pulse is stored in a sample and hold circuit until the next QRS complex occurs The continuous evaluation of the QT time is done according to the empirically found dependency of the QT time upon the RR interval We used an equation given by Ashman [2]

$$QT = K \log (10[RR + 0.07])$$

Factor K the importance of which will be discussed below can easily be found by measuring the RR interval and the QT time in the patient s electrocardiogram (ECG) when starting monitoring In detail evaluation of the QT time (QT) is done by a diode function generator (DFG) that is controlled by an analog signal being proportional to the averaged cycle length ($\overline{RR}$) This signal is the average of all cycles occurring within the antecedent 10 seconds Finally the RR interval (Fig 2 ramp pulses 2 3) and the evaluated QT time (Fig 2 horizontal line 2 3) are compared in a comparator Premature beats interrupting the T wave of the antecedent beat (R on T phenomenon) are obviously characterized by ramp pulses with an amplitude being smaller than the output level of the DFG i e the coupling interval is smaller than the evaluated QT time In such a case an alarm signal starting an ECG recorder is given by the comparator A special storing system is used for delaying the patient s ECG in order to record the ECG period preceding the alarming event All ectopic beats detected in this wav are summarized and their frequency is registered on a trend recorder

Factor K is set by use of a potentiometer that regulates the percentage of voltage applied to the comparator from the DFG Thus it is possible to choose different degrees of prematurity For

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Table I Variation of factor K during a day in eight patients. Factor K was evaluated according to the equation of Ashman[12] using the mean of three cycle lengths. In patient RH determination of K was additionally done using one cycle length. The results demonstrate the greater variability of K in atrial fibrillation when based upon merely one cycle length

Patient age sex	*Rhythm*	*Day of measurement*	*Number of measurements*	$\bar{K}$ *± standard deviation*	*Relative standard deviation (per cent)*	*Ranges of K*
FH 56 yrs male	SR	1	27	0.3765 ± 0.0136	± 3.63	0.3519 to 0.4138
		3	26	0.3851 ± 0.0069	± 1.80	0.3711 to 0.3938
HS 30 yrs. male	SR	1	10	0.4013 ± 0.0122	± 3.04	0.3835 to 0.4187
	LBBB	10	17	0.3871 ± 0.0120	± 3.08	0.3631 to 0.4037
MD 27 yrs. female	SR	1	13	0.4122 ± 0.0141	± 3.43	0.3962 to 0.4458
	LBBB	5	34	0.4455 ± 0.0093	± 2.09	0.4192 to 0.4705
		7	10	0.4381 ± 0.0210	± 4.80	0.4155 to 0.4674
KL 44 yrs male	SR	1	17	0.3519 ± 0.0100	± 2.86	0.3406 to 0.3732
HK 72 yrs. male	SR	1	21	0.4255 ± 0.0119	± 2.82	0.3994 to 0.4380
		3	15	0.4409 ± 0.0100	± 2.45	0.4275 to 0.4565
MW 29 yrs female	SR	1	10	0.3440 ± 0.0100	± 2.91	0.3308 to 0.3590
HZ 39 yrs male	AF	1	40	0.4359 ± 0.0132	± 3.03	0.4066 to 0.4601
		3	68	0.4549 ± 0.0193	± 4.25	0.4208 to 0.5020
RH 69 yrs male	AF	1	46	0.4812 ± 0.0208	± 4.32	0.4486 to 0.5205
				Determination of K based on only one cycle length		
				0.5056 ± 0.0634	± 12.53	0.3816 to 0.6429

SR = sinus rhythm AF = atrial fibrillation LBBB = left bundle branch block

Results

The method described is primarily based upon the evaluation of the QT time according to any of the empirical equations in the literature all containing a constant factor[12-27]. For continuous monitoring it is a prerequisite that this factor often called K remains constant during the period of monitoring. Thus our first objective was to investigate the variability of factor K which was done in eight patients during a period of 16 to 24 hours of monitoring. The results are presented in Table I. Factor K was calculated by use of Ashman's equation with the RR interval being based on the average of three preceding cycles. The following abbreviations were used: K i.e. all factors K observed, K i.e. the initial factor K when starting monitoring, and $\bar{K}$ i.e. the mean of all K for a single patient.

The results show only a slight variability of factor K. The relative standard deviation (coefficient of variation) was up to 4.8 per cent of $\bar{K}$ in patients in sinus rhythm with a mean of 3.0 per cent. However it was higher in patients with atrial fibrillation (3.9 per cent). In one patient with atrial fibrillation factor K was additionally calculated on the basis of only one preceding cycle. Under these conditions there was a great variability of K, the relative standard deviation being 12.5 per cent of $\bar{K}$. The maximal and minimal values of K in the whole group of patients (the calculation based on three cycles) was plus 9.9 per cent and minus 6.35 per cent of the corresponding $\bar{K}$. In patients with atrial fibrillation the range was larger (plus 10.35 per cent and minus 7.50 per cent). The greatest divergencies of K from $\bar{K}$ were seen in atrial fibrillation when K was based only on one cycle length.

As the QT time at a given heart rate is proportional to factor K the divergencies of the evaluated QT time from the measured QT time will be as great as the relative divergencies of K from K. In Fig. 3 is shown the divergencies of the evaluated from the measured QT time in one patient over a longer period. Both correspond well to each other.

In order to demonstrate the advantage of the method used compared to another one a horizontal line is shown in Fig. 3 representing a fixed QT time manually adjusted at the beginning of monitoring. With the change of heart rate great divergencies between the actual QT time and the fixed QT level are evident. This is also the case when using 50 per cent of the average cycle

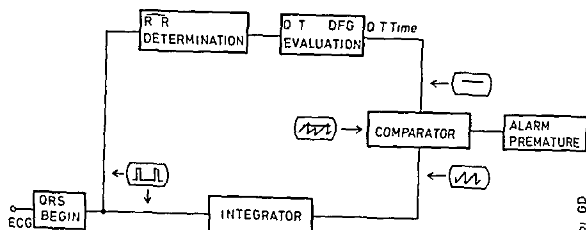


Fig 1 Block diagram of the analog computer for detection of the R on T phenomenon A description of its mode of action is given in the text (DFG i e diode function generator)

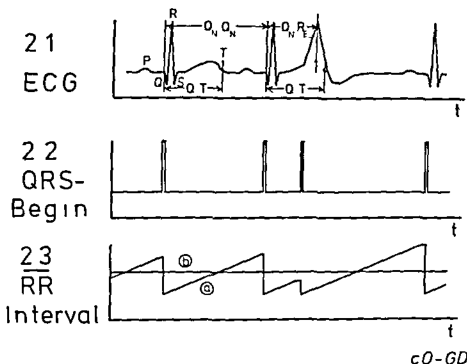


Fig 2 2 1 The patient s ECG demonstrating a ventricular ectopic beat with the R on T phenomenon 2 2 the ECG signal after transformation to short rectangular impulses corresponding to the onset of the QRS complex 2 3 the duration of the ascent of the ramp impulse (signal *a*) corresponds to the actual RR interval signal *b* represents the evaluated QT time Both signals are compared in a comparator As soon as the maximum of the ramp impulse (signal *a*) is smaller than the QT level (signal *b*) a R on T phenomenon is signaled

easier determination of K a two channel oscilloscope can be used with a triggered ECG signal on one channel and on the other channel two measuring marks corresponding to the beginning of the QRS complex and to the evaluated end of the T wave Thus the correct setting of factor K can easily be checked To detect different degrees of prematurity simultaneously, several comparators can be used In combination with a multichannel trend recorder the different registrations can be recorded separately

As there were not reports on changes of factor K during a day we started with determinations of K in patients monitored in a coronary care unit Monitor strips were recorded each 30 to 60 minutes at a speed of 50 mm per second After measuring the averaged RR interval (three cycles) and the corresponding QT time factor K was evaluated according to the equation of Ashman[1] In one patient with atrial fibrillation, factor K was additionally calculated on the basis of only one cycle length in order to determine the variability of K as a function of the number of cycle lengths measured

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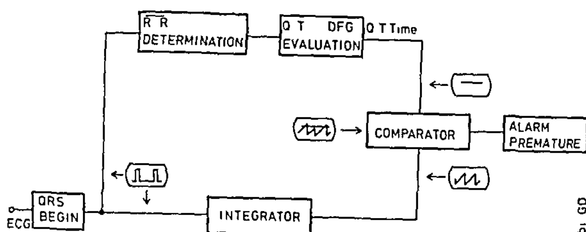


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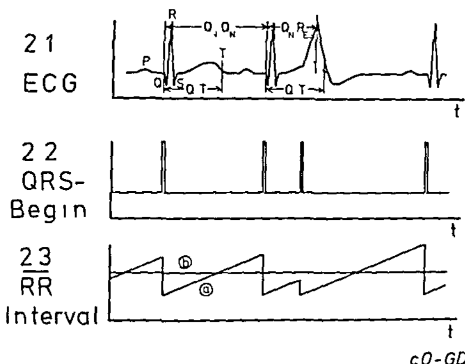


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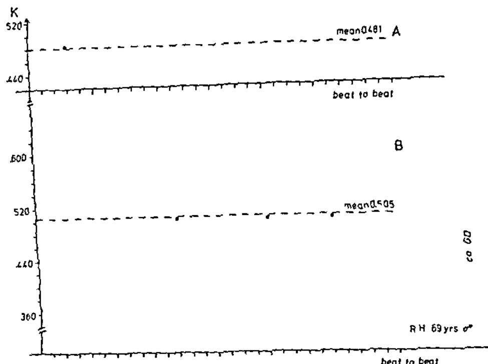


Fig 5 Variability of factor K evaluated according to Ashman in a patient with atrial fibrillation *A* shows the variability of K when the calculation was upon the average of three preceding cycles. *B* greater variability of K when based upon one cycle length.

of prematurity of 0 60 to 0 85[7, 1] In experimental myocardial infarction ventricular bigeminy with varying coupling interval ventricular tachycardias and the R on T phenomenon were alone or altogether highly predictive of ventricular fibrillation [6, 2] Each of these warning arrhythmias had a 75 per cent incidence of ventricular fibrillation Ectopic beats with the R on T phenomenon leading to ventricular fibrillation were often preceded by similar beats not provoking fibrillation at once[4, 22] Thus it is important to detect the earliest ectopic beats occurring in the vulnerable period However continuous observation of the monitor by the medical staff is not reliable for detection of rare events [3, 2]

In principle it is possible to evaluate the index of prematurity continuously after direct measurement of the QT time by a computer[2, 31] However the reliability of this method depends on the exact recognition of the end of the T wave which usually asks for a digital computer Difficulties may arise because of variations in the slope of the T wave A simpler way for detecting the R on T phenomenon is to use a fixed though adjustable QT time[26] However this does not take into account that the QT time changes according to heart rate For instance a spontaneous increase of heart rate from 60 per minute to 100 per minute leads to consecutive changes of the QT time of as much as 20 per cent In such a case a fixed QT time would give a lot of false positive alarms whereas in the opposite case with slowing down of the heart rate there would be false negative results Therefore this method demands frequent readjustment of the QT time as soon as the heart rate changes A third method is to detect all beats falling within the first half of the cardiac cycle[15] However the QT time approximates 50 per cent of the RR interval only within a small range of heart rate

In order to avoid these disadvantages an analog circuit independent of direct measurement of QT time was developed It allows automatic evaluation of the QT time according to heart rate in a diode function generator It is based on the fact that the QT time is depending on two variables i e heart rate and factor K[12, 14, 27] The general form of the different equations reads as follows

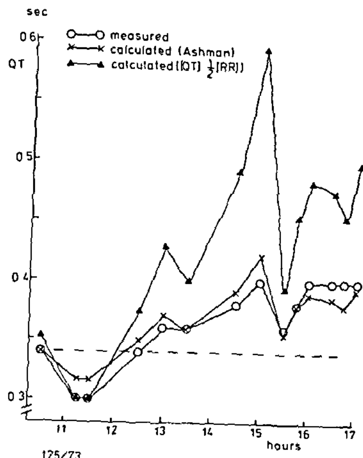


Fig 3 Comparison of the measured and the evaluated QT time in a patient during monitoring In addition to the values according to the equation of Ashman QT is given according to the equation QT = 0 5 RR The dashed horizontal line represents a fixed QT level adjusted at the beginning of monitoring

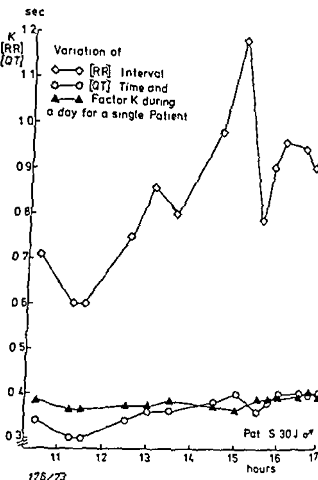


Fig 4 Factor K in a patient with marked variation of the RR interval

length as a criterion for detecting early premature beats [2,15]

Fig 4 shows the constancy of K in a patient with marked variations of heart rate The evaluated QT time was in good agreement with the actual one The standard error of the divergence of K_n from $\overline{K}_n$ was 3 28 per cent of $\overline{K}_n$ Maximal and minimal divergencies of K_n from $\overline{K}$ were up to ±5 0 to 5 5 per cent of $\overline{K}_n$ The greater variability of K in atrial fibrillation when calculated on only one cycle compared to three cycles is shown in Fig 5

Testing of the analog computer model was done by use of tape recorded ECG's First, these investigations were done in the laboratory by mixing premature artificial impulses to the recorded ECG The developed circuit gave exact alarms as soon as a premature impulse fell within the evaluated QT time When monitoring coronary care patients with this device the same results were received Difficulties of detecting premature beats in the patient s ECG were due to poor ECG signals or noise leading to false recognition in the trigger unit False positive results were due to the recognition of artifacts and of T waves as QRS complexes whereas low amplitude of ectopic beats could lead to false negative results False negative detection of normal or ectopic beats with low amplitudes can be controlled by an additional comparator which gives an alarm as soon as the ramp pulse exceeds a certain upper limit This can either mean a missing QRS complex (asystole A V block) or a nontriggered QRS with low amplitude By starting an ECG recorder this can easily be checked by the medical staff

Discussion

Mortality of patients due to rhythm disturbances during the first days of an acute myocardial infarction has been reduced by coronary care units [6,8,16,18] The significance of the R on T phenomenon provoking ventricular tachycardia or fibrillation is well known [6,10,18,19] Experimental studies as well as clinical observations agree that the dangerous phase during which ventricular fibrillation usually occurs is localized at an index

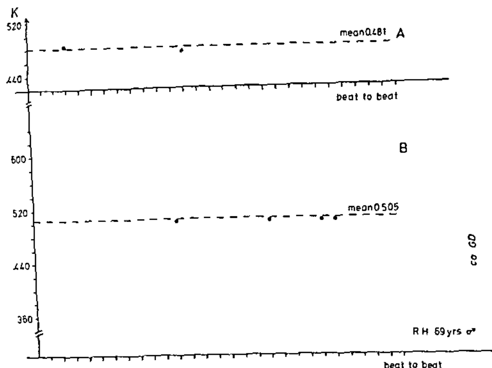


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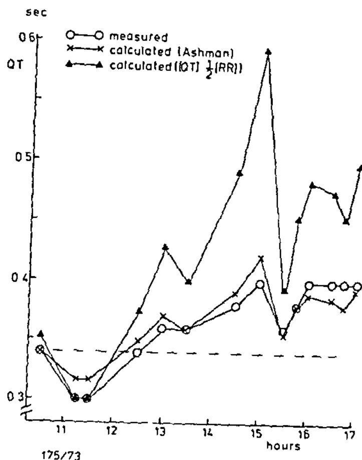


Fig 3 Comparison of the measured and the evaluated QT time in a patient during monitoring In addition to the values according to the equation of Ashman QT is given according to the equation QT = 0 5 RR The dashed horizontal line represents a fixed QT level adjusted at the beginning of monitoring

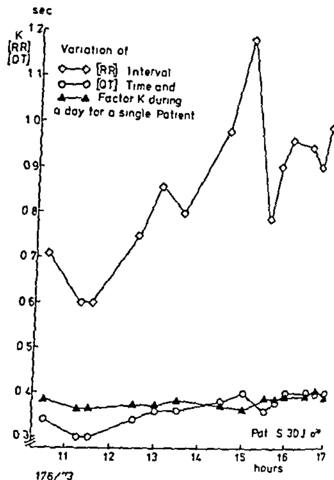


Fig 4 Factor K in a patient with marked variation of the RR interval

length as a criterion for detecting early premature beats [2, 15]

Fig 4 shows the constancy of K in a patient with marked variations of heart rate The evaluated QT time was in good agreement with the actual one The standard error of the divergence of K_n from $\overline{K}_n$ was 3 28 per cent of $\overline{K}$ Maximal and minimal divergencies of K from $\overline{K}$ were up to ±5 0 to 5 5 per cent of $\overline{K}_n$ The greater variability of K in atrial fibrillation when calculated on only one cycle compared to three cycles is shown in Fig 5

Testing of the analog computer model was done by use of tape recorded ECG s First these investigations were done in the laboratory by mixing premature artificial impulses to the recorded ECG The developed circuit gave exact alarms as soon as a premature impulse fell within the evaluated QT time When monitoring coronary care patients with this device the same results were received Difficulties of detecting premature beats in the patient's ECG were due to poor ECG signals or noise leading to false recognition in the trigger unit False positive results were due to the recognition of artifacts and of T waves as QRS complexes whereas low amplitude of ectopic beats could lead to false negative results False negative detection of normal or ectopic beats with low amplitudes can be controlled by an additional comparator which gives an alarm as soon as the ramp pulse exceeds a certain upper limit This can either mean a missing QRS complex (asystole A V block) or a nontriggered QRS with low amplitude By starting an ECG recorder this can easily be checked by the medical staff

Discussion

Mortality of patients due to rhythm disturbances during the first days of an acute myocardial infarction has been reduced by coronary care units [6, 8, 16, 18] The significance of the R on T phenomenon provoking ventricular tachycardia or fibrillation is well known [6, 10, 15, 19] Experimental studies as well as clinical observations agree that the dangerous phase during which ventricular fibrillation usually occurs is localized at an index

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$$QT = QT (RR \ K)$$

Factor K, which is sometimes called corrected QT or QT_c, is different in cardiac hypertrophy,[27,33] myocardial infarction[27,33,34] electrolyte disturbances,[27,34] digitalis or quinidine therapy,[27,34] and depends on age and sex[7,33,34] Elek and co workers[11] showed in *many cases that the individual* factor K was constant in different situations over a wide range of heart rate During the first six weeks of myocardial infarction, there is a gradual decline of K from week to week[34] *Different localizations of myocardial* damage caused different degrees of prolongation of K[34] A major problem is that rapid changes of heart rate such as in paroxysmal tachycardia, are related to a relative prolongation of the QT time within the *first seconds* in normal persons[29] During recovery from exercise the RR interval lengthened much faster than the QT interval[2,29]

Our observations are in accord with these results However up to now there have not been reports on the daily fluctuations of factor K We could demonstrate that there are only small variations of K during 16 to 24 hours of monitoring Therefore, *it is possible to evaluate* the QT time according to an empirical equation We preferred the one given by Ashman[12] as it is said to show better correspondence to the real QT time in the low and high range of heart rate, as for *instance the equation of Bazett*[13]

The relative change of the standard error compared to the average value of K was not higher than 4 8 per cent in patients in sinus rhythm whereas in patients on atrial fibrillation *this was slightly higher Changes of heart rate* may be faster than the consecutive changes of QT time Therefore it is important to use the average of several cycle lengths for evaluating QT time This is especially urgent in patients with atrial *fibrillation* (Fig 5)

As the real factor K ($\overline{K}$) is not known when starting monitoring there may be an appreciable divergence between $\overline{K}$ and K However as K represents one of all K its divergence will usually be not more than the range of the standard error of K

The likelihood *of ventricular tachycardia or* fibrillation provoked by an early premature beat increases gradually with shorter coupling intervals, and is highest at an index of prematurity of 0 60 to 0 85 Therefore it is reasonable to choose an index of *prematurity* close to 1 0 in order not to miss any potentially dangerous beat Additionally, *it is possible to set* several limits by use of more than one comparator

A higher rate of false positive and false negative registrations is to be expected in atrial fibrillation as QT varies from beat to beat nearly *impredictably, whereas the* evaluated QT time depends on the average of the heart rate However, it has to be considered that even with a digital computer it may be impossible to measure the QT time as atrial fibrillatory waves merge with the T wave in an indistinguishable manner

In this context it should be remembered that *the exact measurement of the* QT *time is often* difficult even for the experienced electrocardiologist because of the indiscernability of the end of the T wave in some registrations Thus a varying degree of measurement could not be done in some *of our patients Variability of the measured* QT time and, thus, of factor K may, therefore not be totally due to a biologic variability but in some part to difficulties of defining the exact end of the T wave

Our present experiences proved this new device to be a reliable and simple method for detection of the R on T phenomenon

Summary

The detection of premature ectopic beats coinciding with the T wave of the antecedent beat is important for patient monitoring *In the method* described here, the difficulties of direct measurement of QT time are avoided by evaluating the changes of QT time according to heart rate by use of a diode function generator An analog circuit is used for comparing *the computed QT time* with the coupling interval of successive beats In case of a R on T phenomenon an alarm is given The frequency of alarms is registered on a trend recorder The method is based on empirical equations *which all contain a constant factor* Our investigations showed that the variability of this factor during longer periods of monitoring was small enough to allow sufficient exactness of the evaluation procedure

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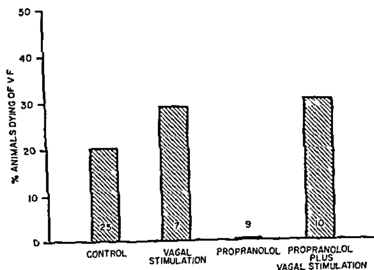


Fig 1 The effect of vagal stimulation propranolol pretreatment and propranolol plus vagal stimulation on the incidence of death due to ventricular fibrillation after occlusion of the anterior descending coronary artery The numbers within the histograms are the number of animals in each group

II) blood pressure and the right ventricular contractile force on a Beckman Dynograph Indices of cardiovascular function were monitored for at least a one hour period following coronary occlusion

Four types of experiments were performed to determine the effect of autonomic neural factors on the cardiovascular changes induced by coronary occlusion

1 Control type coronary occlusion performed on twenty five animals with all nerves intact

2 Vagal stimulation type coronary occlusion performed on seven animals in which the distal ends of the sectioned cervical vagus nerves were electrically stimulated with bipolar platinum electrodes Stimulation was begun 10 minutes prior to occlusion and maintained for the duration of the experiment Parameters of stimulation were 15 Hz 1 5 msec impulse duration and 2 to 8 volts Voltage was determined by the heart rate response and was adjusted to decrease the sinus rate to about 100 beats per minute

3 Propranolol type coronary occlusion performed in nine animals in which d l propranolol was administered as a dose of 0 75 mg per kilogram intravenously ten minutes prior to ligation

4 Propranolol plus vagal stimulation type Coronary occlusion performed in ten animals in which d l propranolol was administered as an average dose of 0 75 mg per kilogram intravenously (range of 0 5 to 1 0 mg per kilogram) twenty minutes prior to ligation Vagal stimulation was performed as described in the Type 2 experiments

The following drugs were used alpha chloralose (Establissements Kuhlmann Paris France) decamethonium bromide solution (Burroughs Wellcome Research Triangle Park N C) and d l propranolol HCl (Sigma Chemical Co St Louis Mo) Alpha chloralose was dissolved by heating it in distilled water the solution was cooled to 37 C before use The d l propranolol HCl was dissolved in 0 85 per cent sodium chloride solution Doses of drugs were calculated and administered as the respective salt

The data were analyzed by paired comparisons and grouped Student s t tests Chi square analysis for a 2 by 2 contingency with the Yates correction was utilized for the death rate data The criterion used for significance was $p<0.05$

Results

Occlusion performed in 25 control animals initially produced significant decreases in heart rate blood pressure and contractile force (Table I) Subsequently each animal exhibited ventricular arrhythmias and five out of 25 died from ventricular fibrillation (Fig 1) The arrhythmia was characterized by either unifocal or multifocal

Effect of autonomic neural influences on the cardiovascular changes induced by coronary occlusion*

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The importance of neural factors to the development of arrhythmias associated with coronary heart disease in patients has recently been stressed by Pantridge and colleagues [1, 2] They reported a high incidence of autonomic disturbance at the onset of acute myocardial infarction and suggested that this imbalance was responsible for the lethal arrhythmias that occur They also suggested that studies directed toward the correction of the autonomic disturbance are likely to be more rewarding than the investigation of the prophylactic value of antiarrhythmic agents with an action similar to lidocaine [2]

In an experimental evaluation of this approach to treatment, we have previously shown that removal of efferent vagal tone by either atropine or bilateral vagotomy significantly increases the incidence of fatal ventricular fibrillation after coronary occlusion [3] In addition, this 'protective effect' of vagal tone is independent of changes in heart rate Similar findings have been observed by others [4, 5] In continuation of these studies we set out to determine whether (1) increasing vagal tone would further aid in protecting the heart from the deleterious electrical effects of coronary occlusion and (2) administering propranolol to prevent the sympathetic disturbance would modify the deleterious changes induced by coronary occlusion

Methods

Cats unselected as to sex and ranging in weight from 1 5 to 3 9 kilograms were used for these experiments They were anesthetized with alpha chloralose (70 to 75 mg per kilogram, and artificially ventilated with room air The respirator was set at a tidal volume of 20 to 25 c c per kilogram and at a rate of 22 breaths per minute The femoral artery and vein were catheterized for recording blood pressure and for administering drugs respectively All animals were immobilized with decamethonium bromide (0 25 mg per kilogram intravenously) every 45 to 60 minutes Body temperature was maintained between 37 5° C and 38 5° C with an infrared lamp

The procedures for isolating the anterior descending branch of the left coronary artery and measuring cardiac contractile force have been described previously [3] Briefly a right thoracotomy was performed by removing ribs two through five The pericardium was then incised and sutured to the chest wall The anterior descending branch of the left coronary artery was isolated immediately after bifurcation and a ligature placed under the vessel proximal to all branch points The ligature was tied securely at the time total occlusion was desired A calibrated Walton Brodie strain gauge arch was then sutured to the right ventricle for the purpose of measuring myocardial contractile force Continuous recordings were made of the electrocardiogram (Lead

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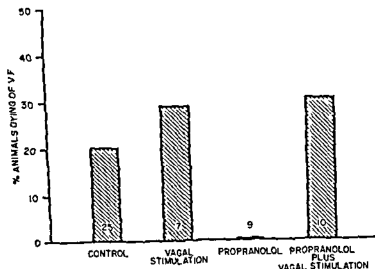


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Results

Occlusion performed in 25 control animals initially produced significant decreases in heart rate blood pressure and contractile force (Table I) Subsequently each animal exhibited ventricular arrhythmias and five out of 25 died from ventricular fibrillation (Fig 1) The arrhythmia was characterized by either unifocal or multifocal

Table I *Influence of vagal stimulation, propranolol and the combination of vagal stimulation and propranolol on the heart rate, blood pressure, contractile force, and cardiac rhythm changes produced by coronary occlusion*

Group	*Before occlusion* Heart rate (beats/min)	Mean blood pressure (mm Hg)	Mean contractile force (Gm tension)	*After occlusion and prior to arrhythmia* Change in heart rate (beats/min)	Change in blood pressure (mm Hg)	Percent change in contractile force	Onset of arrhythmia (min)	Duration of arrhythmia (min)
Control	195.7 ± 6.6 (25)	115.1 ± 4.5 (25)	10.7 ± 0.6 (18)	−22.9 ± 4.4 (25)	−19.2 ± 2.4 (25)	−21.6 ± 6.3 (16)	2.5 ± 0.3 (25)	34.3 ± 1.6 (20)
Vagal Stimulation	102.8 ± 5.4† (7)	89.6 ± 9.8† (7)	9.1 ± 0.5 (7)	+1.7 ± 1.7† (7)	−11.4 ± 3.3 (7)	−43.3 ± 5.9 † (7)	4.8 ± 0.8† (7)	41.0 ± 5.4 (4)
Propranolol	146.7 ± 6.0† (9)	97.3 ± 11.5 (9)	8.0 ± 0.9† (8)	−14.5 ± 3.4 (9)	−16.7 ± 5.1 (9)	−16.1 ± 6.1 (8)	2.0 ± 0.2 (9)	21.7 ± 3.5† (9)
Vagal Stimulation Plus propranolol	90.4 ± 3.1† (10)	65.5 ± 5.2† ‡ (10)	6.7 ± 0.7† (10)	−1.7 ± 0.9† (10)	−11.9 ± 2.3 (10)	−10.8 ± 6.2‡ (10)	4.8 ± 0.6† (9)	17.0 ± 0.5† ‡ (5)

Numbers are means ± S E

Numbers in parentheses indicate number of animals in each group

p < 0.05 with paired comparisons (comparison was made between data obtained during post occlusion period and data obtained during pre occlusion period)

†p < 0.05 with group comparisons (comparison was made between data obtained with either vagal stimulation group, propranolol group or vagal stimulation plus propranolol group versus control group)

‡p < 0.05 with group comparisons (comparison was made between data obtained with vagal stimulation plus propranolol group versus vagal stimulation group)

premature ventricular beats, no evidence of escape beats or heart block was observed. The time to onset of the arrhythmia was quite consistent as was the duration of the arrhythmia in those animals that recovered (Table I).

The summarized data of Table I includes 20 control experiments described in our first study.[3] Five additional control experiments were performed for this study and the electrocardiogram (ECG), blood pressure and contractile force traces of one of these appears as Fig 2. Prior to occlusion, normal sinus rhythm was present at a rate of 207 beats per minute (Panel A). Two minutes after occlusion there was a decrease in rate to 187 beats per minute as well as a decrease in contractile force (Panel B). At this point the animal still exhibited sinus rhythm although S-T segment changes occurred. At 2.5 minutes after occlusion a severe ventricular arrhythmia ensued (Panel C) which continued for 28 minutes, at this time normal sinus rhythm reappeared and remained for the duration of the observation period (Panel D).

The cardiovascular changes produced by coronary occlusion in seven animals in which constant bilateral vagal nerve stimulation was employed are summarized in Table I. Vagal nerve stimulation significantly reduced the pre occlusion heart rates and blood pressures of these animals but did not affect myocardial contractility. Within minutes after occlusion, both blood pressure and contractile force decreased significantly, and the decrease in force was significantly greater than the decrease in force observed in the control animals. Since sinus rate was near its nadir prior to occlusion (as a consequence of vagal stimulation) occlusion did not evoke any further decline in rate. Subsequently each animal developed a disturbance in cardiac rhythm and two out of seven of these animals died from ventricular fibrillation. The percentage that died was similar to the percentage that died in the control group (Fig 1). One of the seven animals died from hypotension 14 minutes after occlusion. Vagal stimulation increased the time to onset of the arrhythmia but had no effect on the duration of the arrhythmias (Table I).

A representative experiment illustrating the changes in ECG, blood pressure and contractile force appears as Fig 3. Prior to occlusion, but

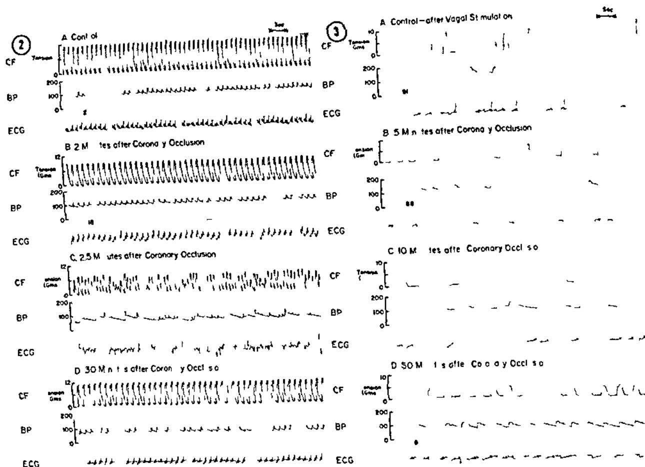


Fig 2 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in a control animal with all nerves intact and functional Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 2 2 5 and 30 minutes after coronary occlusion respectively

Fig 3 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in an animal during electrical stimulation of the vagus nerves Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 5 10 and 50 minutes after coronary occlusion respectively

during vagal stimulation normal sinus rhythm was present with a rate of 91 beats per minute (Panel A) Five minutes after occlusion sinus rhythm was still present although a large widening of the QRS complex was apparent as well as a large reduction in contractile force (Panel B) Ten minutes after occlusion frequent ventricular beats developed (Panel C) and these continued for an additional 40 minutes At the 50 minute mark (Panel D) some sinus beats appeared associated with some junctional escape and fusion beats

Blockade of cardiac adrenergic beta receptors with propranolol was performed in nine animals and the data are also summarized in Table I The pre occlusion heart rates and cardiac contractile force values of these animals were significantly less than the corresponding values of the control animals while both groups had similar pre occlusion blood pressures Occlusion produced the usual decreases in heart rate blood pressure and contractile force as well as ventricular arrhythmias

None of the animals in which propranolol was administered developed fatal ventricular fibrillation (Fig 1) However this difference from control death rates was not statistically significant ($p>0.05$) The most significant finding was that propranolol pretreatment resulted in an arrhythmia that was shorter in duration than that observed in either of the other two groups (Table I) A representative experiment illus

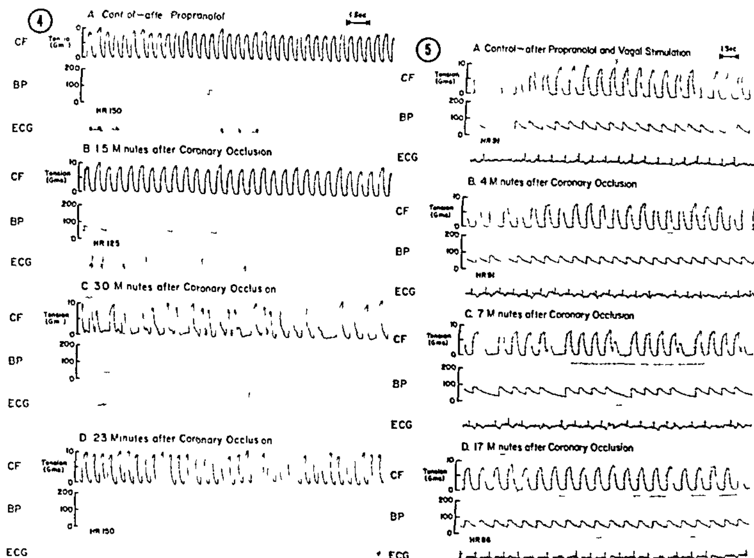


Fig 4 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in an animal pretreated with propranolol (0 75 mg per kilogram) Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 1 5 3 and 23 minutes after coronary occlusion respectively

Fig 5 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in a propranolol pretreated animal (0 75 mg per kilogram) during electrical stimulation of the vagus nerves. Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 4 7 and 17 minutes after coronary occlusion respectively

trating this appears as Fig 4 Prior to occlusion sinus rhythm was present with a rate of 150 beats per minute (Panel A) At 1 5 minutes after occlusion there was a decrease in all three indices of cardiovascular function but sinus rhythm was still apparent (Panel B) Three minutes after occlusion a severe ventricular arrhythmia ensued (Panel C) but returned to normal sinus rhythm 23 minutes after occlusion (Panel D) and remained in sinus rhythm for the duration of the observation period (i e 60 minutes)

Since vagal stimulation delayed the onset of the arrhythmia and propranolol pretreatment shortened the duration of the arrhythmia the two procedures were combined and tested for their ability to completely prevent the occurrence of arrhythmias This combination proved to be no better than either procedure alone (Table I) That is arrhythmias occurred in each animal and the time to onset was delayed (as in the group with vagal stimulation alone) and the duration was shortened (as in the group with propranolol pretreatment) The animals given the combined treatment exhibited pre occlusion heart rates blood pressures and contractile force values below those obtained from the control animals Occlusion resulted in a significant decrease in blood pressure but not in either rate or force (Table I) The decrease in force although not significant was not different than that seen in the

control animals Interestingly propranolol pretreatment prevented the severe decreases in contractile force that routinely occur when occlusion is performed in animals with bilateral vagal nerve stimulation The combination of propranolol and vagal stimulation did not decrease the incidence of fatal ventricular fibrillation (i e 3/10 Fig 1) Furthermore two animals died of hypotension 46 and 48 minutes after ligation

A representative experiment illustrating the changes which occur with coronary occlusion in the presence of vagal stimulation and propranolol is shown in Fig 5 Prior to occlusion heart rate was 91 beats per minute and normal sinus rhythm was present (Panel A) At four minutes after occlusion there was a slight decrease in blood pressure and contractile force Sinus rhythm was still present but S T wave changes can be observed (Panel B) Seven minutes after occlusion premature beats have developed (Panel C) and continue for 17 minutes after occlusion At this point a stable sinus rhythm was re established (Panel D)

Discussion

In our previous study we established that removal of cardiac efferent vagal tone by either atropine administration or bilateral cervical vagotomy increases the vulnerability of the infarcted heart to ventricular fibrillation We concluded that the vagus nerves exert a stabilizing effect on the electrical activity of the heart after coronary occlusion In continuation of this work we set out to determine whether this protective effect of the vagus nerves could be augmented by electrically stimulating these nerves to maximal activity Using incidence of ventricular fibrillation as the index of a protective effect our data demonstrates that intense vagal tone does not result in any additional protection for the infarcted heart The incidence of ventricular fibrillation was similar regardless of whether cardiac vagus nerves were being stimulated by external electrical pulses or by the animal per se

On the other hand data obtained from canine studies indicate that enhancing parasympathetic effects on the heart will protect against the development of ventricular fibrillation This is probably due to the fact that the dog in contrast to the cat exhibits minimal vagal tone during the period of coronary occlusion Indeed vagal withdrawal appears to occur as tachycardia is produced by occlusion in this species[4 5 7 10] Of the two species, the cat may be the best experimental model for human infarction Both the cat and human exhibit bradycardia and hypotension during acute myocardial infarction[1 3] The bradycardia in both cases appears to be due to exaggerated vagal tone[1 3 11] The intensity of intrinsic vagal tone seen in cats at the time of infarction appears maximal in terms of protecting the heart from ventricular fibrillation and nothing is gained by augmenting vagal activity above this level This may also be true in man and implies that development of drugs which exaggerate parasympathetic influences during myocardial infarction may not be warranted

In our study vagal stimulation did delay the onset of ventricular arrhythmias This was also true in the study of Myers and colleagues[4] as vagal stimulation delayed the onset of ventricular fibrillation The delay also occurs in animals with hearts paced to rates comparable to those rates observed before vagal stimulation and is therefore not related to the slow heart rate per se[4] An additional finding was that the contractile force of animals with vagus nerves electrically stimulated during coronary occlusion exhibited exaggerated decreases in myocardial contractile force One possible reason for this marked depression in contractile force might be the accentuated interaction between the parasympathetic and sympathetic systems as described by Levy[12] He reported that vagal stimulation produces a much larger depression of left ventricular contractile force in the presence of tonic sympathetic activity than in the absence of tonic sympathetic activity[1] This accentuated antagonism is specific for the adrenergic and cholinergic systems as no potentiation of the negative inotropic effect of vagal stimulation occurs when contractile force is enhanced by a non adrenergic intervention such as aminophylline administration[13] In the case of coronary occlusion tonic sympathetic activity has been shown to be high[1 3] and vagal stimulation may interact with sympathetic drive to produce the pronounced falls in contractile force observed in our study

In regard to cardiac adrenergic mechanisms blockade of beta adrenergic receptors with propranolol resulted in a shortening of the duration of the arrhythmias This suggests that sympa

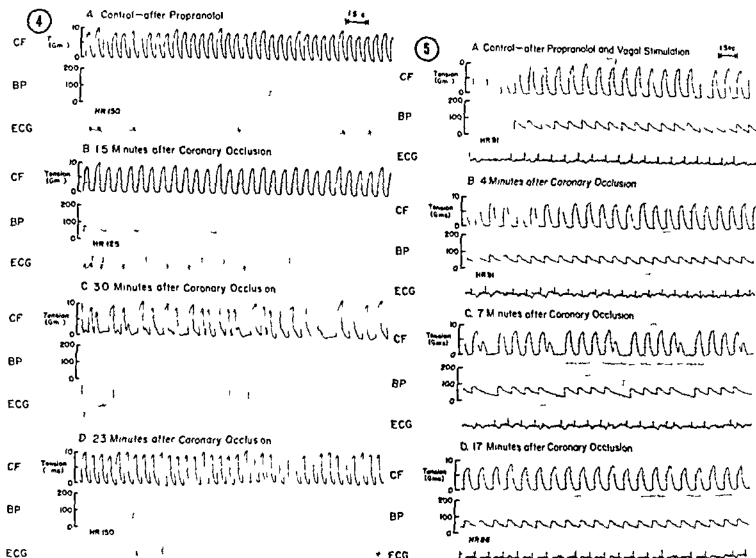


Fig 4 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in an animal pretreated with propranolol (0 75 mg per kilogram) Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 1 5 3 and 23 minutes after coronary occlusion respectively

Fig 5 Effects of coronary occlusion on contractile force (CF) blood pressure (BP) and electrocardiogram (ECG) in a propranolol pretreated animal (0 75 mg per kilogram) during electrical stimulation of the vagus nerves Panel *A* control recordings panels *B* *C* and *D* recordings obtained at 4 7 and 17 minutes after coronary occlusion respectively

trating this appears as Fig 4 Prior to occlusion sinus rhythm was present with a rate of 150 beats per minute (Panel A) At 1 5 minutes after occlusion there was a decrease in all three indices of cardiovascular function but sinus rhythm was still apparent (Panel B) Three minutes after occlusion a severe ventricular arrhythmia ensued (Panel C) but returned to normal sinus rhythm 23 minutes after occlusion (Panel D) and remained in sinus rhythm for the duration of the observation period (i e , 60 minutes)

Since vagal stimulation delayed the onset of the arrhythmia and propranolol pretreatment shortened the duration of the arrhythmia the two procedures were combined and tested for their ability to completely prevent the occurrence of arrhythmias This combination proved to be no better than either procedure alone (Table I) That is arrhythmias occurred in each animal and the time to onset was delayed (as in the group with vagal stimulation alone) and the duration was shortened (as in the group with propranolol pretreatment) The animals given the combined treatment exhibited pre occlusion heart rates blood pressures, and contractile force values below those obtained from the control animals Occlusion resulted in a significant decrease in blood pressure but not in either rate or force (Table I) The decrease in force although not significant was not different than that seen in the

control animals Interestingly propranolol pretreatment prevented the severe decreases in contractile force that routinely occur when occlusion is performed in animals with bilateral vagal nerve stimulation The combination of propranolol and vagal stimulation did not decrease the incidence of fatal ventricular fibrillation (i e 3/10 Fig 1) Furthermore two animals died of hypotension 46 and 48 minutes after ligation

A representative experiment illustrating the changes which occur with coronary occlusion in the presence of vagal stimulation and propranolol is shown in Fig 5 Prior to occlusion heart rate was 91 beats per minute and normal sinus rhythm was present (Panel A) At four minutes after occlusion there was a slight decrease in blood pressure and contractile force Sinus rhythm was still present but S T wave changes can be observed (Panel B) Seven minutes after occlusion premature beats have developed (Panel C) and continue for 17 minutes after occlusion At this point a stable sinus rhythm was re established (Panel D)

Discussion

In our previous study we established that removal of cardiac efferent vagal tone by either atropine administration or bilateral cervical vagotomy increases the vulnerability of the infarcted heart to ventricular fibrillation We concluded that the vagus nerves exert a stabilizing effect on the electrical activity of the heart after coronary occlusion In continuation of this work we set out to determine whether this protective effect of the vagus nerves could be augmented by electrically stimulating these nerves to maximal activity Using incidence of ventricular fibrillation as the index of a protective effect our data demonstrates that intense vagal tone does not result in any additional protection for the infarcted heart The incidence of ventricular fibrillation was similar regardless of whether cardiac vagus nerves were being stimulated by external electrical pulses or by the animal per se

On the other hand data obtained from canine studies indicate that enhancing parasympathetic effects on the heart will protect against the development of ventricular fibrillation This is probably due to the fact that the dog in contrast to the cat exhibits minimal vagal tone during the period of coronary occlusion Indeed vagal withdrawal appears to occur as tachycardia is produced by occlusion in this species[4,5,7,10] Of the two species the cat may be the best experimental model for human infarction Both the cat and human exhibit bradycardia and hypotension during acute myocardial infarction [3] The bradycardia in both cases appears to be due to exaggerated vagal tone [3,11] The intensity of intrinsic vagal tone seen in cats at the time of infarction appears maximal in terms of protecting the heart from ventricular fibrillation and nothing is gained by augmenting vagal activity above this level This may also be true in man and implies that development of drugs which exaggerate parasympathetic influences during myocardial infarction may not be warranted

In our study vagal stimulation did delay the onset of ventricular arrhythmias This was also true in the study of Myers and colleagues as vagal stimulation delayed the onset of ventricular fibrillation The delay also occurs in animals with hearts paced to rates comparable to those rates observed before vagal stimulation and is therefore not related to the slow heart rate per se[6] An additional finding was that the contractile force of animals with vagus nerves electrically stimulated during coronary occlusion exhibited exaggerated decreases in myocardial contractile force One possible reason for this marked depression in contractile force might be the accentuated interaction between the parasympathetic and sympathetic systems as described by Levy [2] He reported that vagal stimulation produces a much larger depression of left ventricular contractile force in the presence of tonic sympathetic activity than in the absence of tonic sympathetic activity[13] This accentuated antagonism is specific for the adrenergic and cholinergic systems as no potentiation of the negative inotropic effect of vagal stimulation occurs when contractile force is enhanced by a non adrenergic intervention such as aminophylline administration [3] In the case of coronary occlusion tonic sympathetic activity has been shown to be high[1] and vagal stimulation may interact with sympathetic drive to produce the pronounced falls in contractile force observed in our study

In regard to cardiac adrenergic mechanisms blockade of beta adrenergic receptors with propranolol resulted in a shortening of the duration of the arrhythmias This suggests that sympa

thetic neural activity may be responsible for maintaining electrical instability after myocardial infarction Fowlis and colleagues[16] have also reported that removal of cardiac sympathetic drive by bilateral cardiac sympathectomy significantly reduces the duration of ventricular tachycardia induced by coronary artery occlusion Blocking beta adrenergic receptors with propranolol in the present study did not decrease significantly the incidence of ventricular fibrillation It might be argued that our fibrillation incidence in control animals (i e 20 per cent) was too low to evaluate the influence of beta adrenergic blockade and no form of therapy could conceivably improve the results We have previously shown that fibrillation incidence is high in animals with vagus nerves sectioned[3], 60 per cent or 12 out of 20 animals developed this arrhythmia We therefore, determined fibrillation incidence in 12 vagotomized animals pretreated with propranolol We found that propranolol administration did not significantly reduce the occurrence of this lethal arrhythmia as 33 per cent developed ventricular fibrillation Furthermore when propranolol was combined with vagal stimulation 30 per cent of the animals developed ventricular fibrillation ($p>0.05$) These results clearly demonstrate the ineffectiveness of d,l propranolol in preventing ventricular fibrillation induced by coronary occlusion

The obvious explanation for the inability of beta adrenergic blockade to influence fibrillation incidence is that cardiac sympathetic neural activity is not an important initiating factor in this arrhythmia A less obvious explanation, but more provocative one is that propranolol may not block all adrenergic cardiac synapses Randall and colleagues[11 1] have demonstrated that intravenous administration of 1 mg per kilogram of propranolol fails to prevent arrhythmias produced by electrical stimulation of the ventrolateral cardiac sympathetic nerve in dogs If this nerve carries arrhythmogenic stimuli from the central nervous system during acute myocardial infarction, blocking cardiac beta adrenergic receptors will not provide an accurate assessment of the role of cardiac sympathetic nerve activity in this arrhythmia

Other investigators have also reported that pretreatment with propranolol (1 mg per kilogram intravenously), a dose that blocks fully the chronotropic response of the heart to either stellate ganglion stimulation or isoproterenol[19] fails to significantly alter the fibrillation incidence in dogs subjected to coronary artery occlusion[20 21] Interestingly, doses that are insufficient for fully blocking these receptors (i e, 0 08 and 0 1 mg per kilogram intravenously) have been reported to significantly reduce the incidence of lethal arrhythmias[0 2] The effect occurs in a narrow dose range as 0 2 mg per kilogram intravenously appears to lack this protective activity The mechanism for the protective effect is unclear These small doses were not tried in our study as we were concerned with the effect of total blockade of cardiac adrenergic receptors

Results obtained from our propranolol pretreated animals also indicate that cardiac beta adrenergic receptors are not involved in the negative inotropic negative chronotropic and hypotensive effects induced by coronary occlusion Decreases in these parameters were similar regardless of whether or not the animals had received propranolol

Finally, our data indicates that little is gained by combining the two procedures that appear beneficial in terms of arrhythmia duration (i e vagal stimulation and propranolol pretreatment) On the other hand some advantage is gained in regard to the contractile force changes as propranolol pretreatment effectively counteracted the pronounced negative inotropic effect of vagal stimulation This supports the idea of Levy[17] that accentuated antagonism occurs between the two divisions of the autonomic nervous system in the heart In the presence of appreciable sympathetic tone vagal stimulation exerts a profound negative inotropic effect but in the absence of sympathetic tone (i e in the presence of propranolol) vagal stimulation exerts a minimal negative inotropic effect

In conclusion our study was undertaken with two purposes in mind first to examine the effect of high vagal tone on the cardiovascular changes induced by coronary occlusion and second to examine the effect of blocking cardiac beta adrenergic receptors on changes induced by coronary occlusion Activation of the vagus nerves delayed the onset of ventricular arrhythmias but did not provide any additional benefit above that seen by leaving the vagus nerves intact and unstimulated by external stimuli Blocking

cardiac beta adrenergic receptors shortened the duration of ventricular arrhythmias and suggests that stimulation of beta adrenergic receptors may be responsible for maintaining electrical instability after occlusion of the anterior descending coronary artery

Summary

The influence of vagal stimulation and/or beta adrenergic receptor blockade on the heart rate blood pressure contractile force and cardiac rhythm was evaluated in chloralose anesthetized cats subjected to occlusion of the anterior descending coronary artery Occlusion performed in 25 control animals produced significant decreases in heart rate (−22 9 ± 4 4 beats per minute) blood pressure (−19 2 ± 2 4 mm Hg) and contractile force (−21 6 ± 6 3 per cent) Death due to ventricular fibrillation occurred in five out of 25 animals Coronary occlusion performed in the presence of vagal nerve stimulation resulted in similar decreases in blood pressure whereas the decreases in contractile force were significantly greater than in control animals In addition the time to onset of the arrhythmias occurring in the vagus stimulated group was increased Death due to ventricular fibrillation was similar to control animals (i e two of seven or 28 per cent) Blockade of beta adrenergic receptors with propranolol (0 75 mg per kilogram) resulted in the usual decreases in rate pressure and force with occlusion but the duration of arrhythmias was shortened The incidence of ventricular fibrillation was not different from that of the control animals The combination of propranolol and vagal stimulation also failed to confer protection against ventricular fibrillation Propranolol was observed to prevent the large decrease in contractile force seen with vagal stimulation These results suggest that (1) increasing vagal tone above the level existing after acute myocardial infarction does not decrease mortality (2) propranolol pretreatment does not affect the incidence of ventricular fibrillation induced by coronary occlusion (3) the duration of the arrhythmia after coronary occlusion is effectively shortened with propranolol and (4) cardiac beta adrenergic receptors do not appear to be involved in the decreases in heart rate blood pressure and contractile force seen with coronary occlusion

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Case reports

Reversal of 'inoperable' pulmonary hypertension

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Severe pulmonary hypertension associated with pulmonary vascular disease has been regarded as a contraindication for surgery in congenital heart disease because of the high operative mortality rate This case report demonstrates the need to follow even those patients presumed to have inoperable heart disease Changing clinical findings over a period of years in this patient indicated the need for thorough re evaluation

Case history

This child was born at approximately 25 weeks gestation weighing 740 grams She had mild idiopathic respiratory distress syndrome severe apneic episodes and hyperbilirubinemia During her initial hospitalization she developed pneumonia A Grade 2/6 machinery type murmur loudest at the left sternal border in the second intercostal space was felt to represent a patent ductus arteriosus (PDA) but this murmur was not heard at the time of discharge from the premature nursery at 10 weeks of age

During her second hospitalization at six months of age for pneumonia a systolic murmur was heard tachycardia was present and heart enlargement with normal pulmonary vascular markings was noted on chest x ray (Fig 1 *A*) Her third hospitalization at age six and a half months was again for pneumonia

She was admitted again at 11 months of age four months following her last episod of recognizable pneumonia in moderate distress with congestive heart failure Chest x ray films showed a few residual signs in the region previously involved with pneumonia and atelectasis (Fig 1 *B*) The pulmonary vascularity was normal Her clinical findings at this time included tachycardia hepatomegaly gallop rhythm, Grade 1/6 blowing systolic murmur at the left sternal border with diastole remaining clear and a markedly increased and unsplit second sound in the pulmonic area There was differential cyanosis of the extremities with acyanotic fingernails and cyanotic toenails. She was digitalized and given diuretics with good clinical improvement Cardiac catheterization after improvement revealed a PDA with bidirectional shunting and severe pulmonary hypertension with markedly elevated pulmonary vascular resistance (Table I) The condition was felt to be inoperable because of the pulmonary vascular obstruction and the absence of a significant left to-right shunt

The social situation was poor and follow up visits were sporadic At age 11 months, clubbing was not described but was observed at 15 and again at 21 months At 35 months she had only clubbing with no definite cyanosis Over the years the murmur became progressively louder and pansystolic At age four years there was a question of a spill-over of the murmur into diastole She was then lost to follow up until age six when her murmur was definitely continuous and the second sound in the pulmonic area only mildly accentuated

She was admitted for her second catheterization at age seven years six years after her initial cardiac catheterization She had a Grade 3/6 continuous murmur typical of a PDA loudest in the second intercostal space in the left midclavicular line and had neither cyanosis nor clubbing Her clinical findings are summarized in Table II representative chest x rays and ECG are shown in Figs 1 *C* and 2

The second cardiac catheterization revealed mildly elevated pulmonary artery pressure no right to-left shunt and a significant left to right shunt at the level of the pulmonary artery

At operation a 6 to 7 mm PDA was found divided and oversewn She tolerated the operation well, had a benign postoperative course and went home on the fourth postoperative day

Discussion

In infants with or without left to right shunts the pulmonary vascular resistance (PVR) falls in early infancy, but even in large ventricular septal defects this has occurred by 12 weeks [2] The larger defects with greater severity of symptoms are at risk of progression to even higher PVR [3] The very late and relatively marked decrease in PVR in our patient requires further consideration There are two pieces of data missing from the first cardiac catheterization the pulmonary artery wedge pressure and the oxygen saturation of the pulmonary vein The latter was assumed to be 96

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Fig 1 Serial chest x rays show (*left*) RUI and LLL pneumonia at six months (Dec 7 1964) (*middle*) LLL atelectasis at 11 months (May 20 1965) and (*right*) mildly increased pulmonary vascularity and prominent main pulmonary artery at seven years of age (Aug 25 1971)

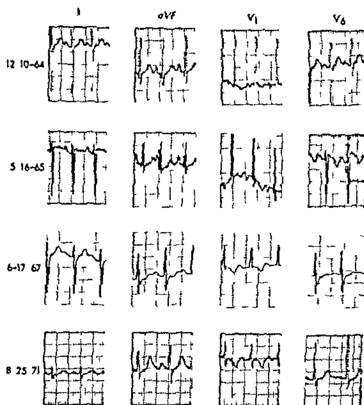


Fig 2 Serial ECG s show the changing patterns from RVH and p pulmonale at six months (Dec 10 1964) RVH with strain and p pulmonale at 11 months (May 16 1965) RVH at three years (June 17 1967) and to CVH at seven years of age (Aug 25 1971)

per cent at the time of the first study, which caused the calculated right to left shunt to be large since the saturation in the descending aorta was only 83 per cent The earpiece oximetry obtained at the conclusion of the catheterization > 85 per cent was probably a valid reflection of the saturation in the ascending aorta and therefore of the pulmonary vein This would indicate intrapulmonary shunting and would imply that pulmonary parenchymal disease was a major cause of the pulmonary hypertension However as can be seen from the alternate calculations in Table I, using the lower pulmonary vein saturation would still yield a negligible left to right shunt and a pulmonary vascular resistance almost equal to the systemic vascular resistance

The calculated net pulmonary vascular resistance for the first catheterization done in 1965 is based on an assumed value of 10 mm Hg for the pulmonary artery wedge pressure (Unfortunately this position of the catheter was not achieved during the first procedure) Judging from the radiologic findings at that time age 11 months (Fig 1 *B*) there was no pulmonary venous hypertension there were no Kerley s B lines or relative hypoperfusion of the lower lobes Calculating the total pulmonary resistance (TPR) the values are extraordinarily high no matter which saturation of the pulmonary vein is used (Table I)

To most clinicians evidence of the early severity and stability of pulmonary hypertension may be found in the physical and ECG findings After the first month of life the patient had no continuous murmur until past five years (Table II) The only murmur was a very soft left sternal border murmur in systole The pulmonic closure was accentuated by six months of age and remained loud throughout the follow up period The ECG s showed an abnormal degree of right ventricular hypertrophy (RVH) from the first tracing at six months (Fig 2) by 11 months there was p pulmonale in addition Marked RVH was still present at three years of age but no p pulmonale Combined ventricular hypertrophy

Table I Cardiac catheterization results

Position	*Pressures*		*Per cent O_2 saturation*		*O_2 content*
	1965	1971	1965	1971	1971
			59	84	12.83
SVC	3	8	60	81	
RA	90/?/4	47/3/8	59	82	
RV	88/58	46/26	67	88	14 01
MPA	70	35			
		11			
PC	90/52		83		
Descending aorta	68				
			85		
Ear oximeter		115/85		97	15 44
Brachial		88			
				97	
Femoral					
Pulmonic/systemic flow ratio	0.9/1†	1.8/1			
	1 4/1‡				
Total pulmonary vascular resistance	6,860†	?87			
(dynes sec. cm)	4 160‡				
Resistance ratio P/S	1/1 5§	1/5			

Mean
†Assuming pulmonary vein saturation of 96 per cent
‡Assuming pulmonary vein saturation of 85 per cent
§Assuming pulmonary wedge pressure of 10 mm Hg

Table II Clinical findings

Age (yr)	*Cyanosis*	*Clubbing*	*Murmur*	P
1/12*	0	0	2/6 continuous	~
?/12	0	0	0	~
6/12	0	0	2/6 short LSB systolic	↑ ↑
11/12	Pink fingers cyanotic toes	0	1/6 short LSB systolic	↑ ↑ ↑
1 3/12*	Mild cyanosis lips and nails	Minimal	1 2/6 upper mid LSB systolic	↑ ↑ ↑ ↑
1 9/12	Mild	Mild	2/6 2nd LSB systolic	↑ ↑
? 11/12	0	Mild	2/6 LSB harsh pansystolic	~
4-4/12	0	0	2/6 moderately harsh diastolic spillover	↑ ↑
6-7/12	0	0	3/6 continuous	↑ ↑
2/12†	0	0	3/6 continuous	↑

1st catheterization
†2nd catheterization

was first suggested at age four and by seven years seemed established

The relationship of pulmonary parenchymal disease to increased pulmonary vascular resistance is well known (cor pulmonale) atelectasis can produce a marked increase in resistance in the involved segment and in addition a secondary increase in the total PVR by *the effects of* hypoxia and hyperpnea This patient had idiopathic respiratory distress in the neonatal period and at six months of age had *major changes of* atelectasis and consolidation on x ray Although there was no clinical evidence of acute pulmonary disease at the time of cardiac catheterization at 11 months there was radiographic evidence of residual parenchymal disease The most unusual aspect of the course of this child s disease is the very slow regression of PVR judged from clinical evidence The most likely *explanation for* the decline in PVR is the resolution of chronic pulmonary parenchymal abnormalities

The other possible explanation for resolution of this patient s pulmonary vascular obstruction is spontaneous improvement unrelated to resolving *parenchymal disease* This has not been reported *previously and* must be regarded as an unlikely

explanation Spontaneous closure of the ductus, if that had occurred early in life, might have led to an improvement in PVR, but the ductus was obviously patent The most likely explanation for the course of events in this patient seems to be slowly resolving parenchymal disease

The importance of these data, regardless of their explanation, lies in the fact that between the ages of 11 months and seven years, the hemodynamics of this patient changed from those associated with severe pulmonary hypertension and bidirectional shunting to mild pulmonary hypertension and pure left to right shunting She therefore, became a candidate for operation which proved successful several years after her condition had been judged inoperable This emphasizes the need for regular follow up of all patients with congenital heart disease, even those whose conditions are considered inoperable

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A demonstration of differential refractoriness within a single fascicle of the human ventricular specialized conduction system

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Recent microelectrode studies [3] performed on canine ventricular specialized conducting systems (VSCS) have shown that refractoriness within a single fascicle of the VSCS increases as the sampling site is moved distally until a region of maximal action potential duration and local refractoriness is reached This latter area has been termed the gate for its electrophysiologic properties determine whether within the VSCS a propagating premature impulse will result in ventricular depolarization

Left bundle branch block (LBBB) in human subjects is an attractive experimental analog to the studies in isolated canine VSCS Our prior studies have demonstrated that in LBBB under specific experimental conditions the ventricles are activated by the right bundle branch (RBB) and can be considered in terms of the VSCS as a monofascicular system Consequently this study was undertaken to determine whether within this monofascicular system it would be possible to demonstrate differential refractoriness

Methods

Fifteen patients whose 12 lead electrocardiograms were diagnostic of LBBB as defined by the New York Heart Association[5] form the basis of this study In addition to LBBB each electrocardiogram demonstrated normal sinus rhythm and a normal PR interval None of the patients had incurred prior myocardial infarction nor were any taking medication known to alter the refractoriness of the atrioventricular conducting system (AVCS)

During right heart catheterization atrial His bundle and ventricular electrograms were recorded by methods previously described [6] The extra stimulus method[7-10] was employed to introduce (via the right atrial catheter) successively more premature square wave cathodal stimuli 1 5 msec in duration and twice diastolic threshold to the atrium near the sinus node until the duration of atrial excitability had been scanned The methodology for stimulation and recording has been recently described in detail [4]

This technique allows independent determination of A V nodal and VSCS refractoriness Although the premature stimulus is applied to the right atrium the resulting His depolarization (H_2) is in fact a premature stimulus applied to the VSCS By analyzing ventricular responses as a function of the interval between His bundle depolarizations of sinus origin (H_1) and the premature His bundle depolarization (H_2) the conduction characteristics and refractoriness of the VSCS could be determined independently of conduction events within the atrium and A V node when the VSCS was more refractory than the atrium or A V node

The following definitions are used in the study

Atrioventricular conducting system (AVCS) The cardiac conduction tissues including the atrioventricular node His bundle right bundle and the two divisions of the left bundle (the anterior superior and posterior inferior) and the distal Purkinje fibers

Ventricular specialized conducting system (VSCS) The entire AVCS below the A V node

Effective refractory period (ERP) of the VSCS

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explanation Spontaneous closure of the ductus if that had occurred early in life, might have led to an improvement in PVR, but the ductus was obviously patent The most likely explanation for the course of events in this patient seems to be slowly resolving parenchymal disease

The importance of these data regardless of their explanation, lies in the fact that between the ages of 11 months and seven years the hemodynamics of this patient changed from those associated with severe pulmonary hypertension and bidirectional shunting to mild pulmonary hypertension and pure left to right shunting She therefore, became a candidate for operation which proved successful several years after her condition had been judged inoperable This emphasizes the need for regular follow up of all patients with congenital heart disease even those whose conditions are considered inoperable

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the three fascicles of the VSCS differs During the stimulation sequence as the $H_1 H_2$ interval was made shorter an abrupt leftward shift in axis was noted in those patients who initially had a normal (−30 to +90°) mean QRS axis The shift ranged from 6° to 68 and persisted until the ERP of the VSCS was exceeded This axis shift indicated that the ERP of the anterior division of the LBB had been exceeded and consequently its contribution to ventricular activation lost Thus after the axis shift ventricular activation was occurring via the RBB which had the shortest ERP of the three divisions of the VSCS The detailed reasoning that led to these conclusions has been previously reported[4]

No changes in mean QRS axis or morphology were noted during the stimulation sequence to suggest that the ERP of the left posterior division was reached Presumably its refractoriness was exceeded at the outset of the stimulation sequence and it thus had the longest ERP of the three fascicles The ERP of the anterior division of the LBB was intermediate between the RBB and the posterior division of the LBB

Two of the fifteen study patients (W M and J T) presented a unique electrophysiologic phenomenon not previously described in human subjects In both patients the VSCS was the most refractory component of the entire AVCS (ERP of the VSCS 485 and 410 msec respectively) After the ERP of the VSCS had been exceeded and A V conduction ceased the antegrade impulse blocked below the His bundle With further shortening of the A A_2 interval the H H interval continued to shorten as well After the H H_2 interval had been shortened to a value 40 to 50 msec less than the ERP of the VSCS conduction to the ventricle unexpectedly resumed (Fig 1) This finding was not noted in the six other LBBB patients with primary VSCS refractoriness nor in any of the some 100 patients with normal electrocardiograms studied in this laboratory by a similar methodology

Fig 2 presents in graphic form this special gap noted in A V conduction It is clear that when conduction from the His bundle to the ventricular resumed the interval between His bundle depolarization and ventricular activation (the $H_2 V_2$ interval) was markedly prolonged typically 100 to 200 msec longer than the H V intervals noted during sinus rhythm Both the duration of the gap (40 to 50 msec) and the $H_2 V_2$ intervals after resumption of conduction (160 to 230 msec) were very similar in both patients

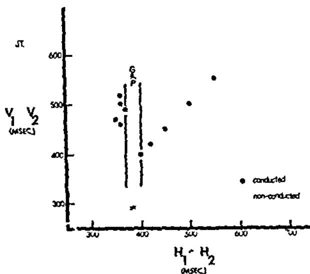


Fig 2 A graph from patient J T illustrates the gap" noted in VSCS conduction The V V intervals are plotted as a function of the H H intervals The symbols used are identified in the lower right hand corner of the graph Conducted beats resulted in ventricular depolarization The non conducted beats identified by x are test impulses which blocked below the His bundle As the H H interval shortens the V V interval shortens as well until the ERP of the VSCS is exceeded at an H H interval of 410 msec The test impulses having H H intervals between 410 and 360 msec do not depolarize the ventricles as represented by the shaded area labeled "gap" At an H H interval of 360 msec ventricular conduction resumes but with markedly prolonged V V times The increase in V V time is necessarily a result of the markedly prolonged H H times (160 230 msec) encountered at these short H H intervals As is clear this phenomenon is entirely independent of events within the A V node

Fig 3 illustrates the long $H_2 V_2$ intervals encountered at the shorter $H_1 H_2$ intervals after A V conduction resumed Following the 'gap in VSCS conduction the morphology of the conducted beat showed the same leftward shift in QRS axis as the premature test beats occurring before the gap indicating once again that ventricular activation was occurring via the RBB With further shortening of the coupling interval, the atrium became refractory in both patients ending the stimulation sequence

Discussion

The extra stimulus method can be used to characterize the conduction properties of cardiac tissue Alterations from normal whether caused by changes in heart rate cardioactive drugs the autonomic nervous system or the effects of cardiac disease can be assessed by this technique as well

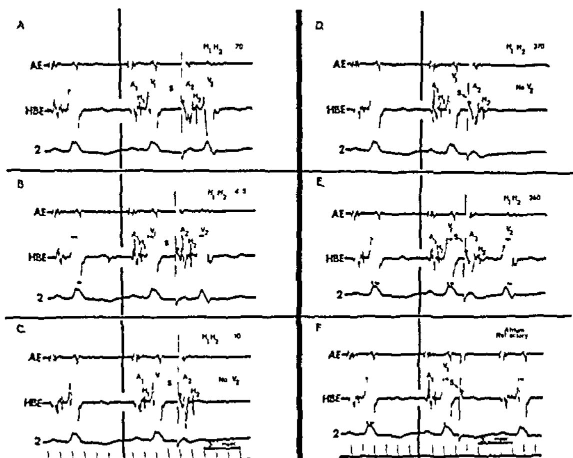


Fig 1 Panels *A* through *F* illustrate the gap noted in the VSCS conduction with progressive shortening of the H H interval In each panel are shown an atrial electrogram (AE) His bundle electrogram (HBE) and ECG Lead 2 Atrial (A) His bundle (H) and ventricular (V) depolarizations are shown The vertical black bar aligns sinus beats preceding the introduction of the test stimulus labeled *S* Time lines at 100 msec intervals are shown at the bottom of panels *C* and *F* and apply to all six panels *Panel A* A is introduced 470 msec after the preceding sinus beat There is no delay in either the A V node or VSCS so that both the H H and V V intervals are 470 msec The H V interval is 70 msec *Panel B* The A A interval has been shortened to 395 msec There is a delay of 20 msec in the A V node and the H H interval is 415 msec A leftward shift in the mean QRS axis of the premature beat has occurred *Panel C* The A A interval is shortened by 5 msec to 390 msec At this H H interval—410 msec—the ERP of the VSCS has been exceeded and conduction of the test impulse fails distal to the His bundle No ventricular complex is seen *Panel D* The A A interval is shortened to 350 msec and the H H interval has shortened to 370 msec Again no ventricular complex is seen *Panel E* The A A interval is now 340 msec and the resulting H H interval has shortened to 360 msec However ventricular conduction has resumed with an H V time of 190 msec The resulting ventricular complex (V) has the same slight leftward shift in mean QRS axis as the V in panel *B* which was at an H H interval slightly in excess of the ERP of the VSCS *Panel F* The stimulus has been made 10 msec earlier and the atrium is now refractory ending the stimulation sequence

The shortest H_1 H_2 interval at which H_2 conducts to the ventricle and results in ventricular depolarization

Results

All 15 patients had normal A H times but prolonged H V intervals (60 to 90 average 73 msec) When the extra stimulus method was applied during sinus rhythm the site of initial refractoriness varied In seven patients, initial refractoriness of either the atrium (five patients) or the A V node (two patients) precluded precise determination of the refractoriness of the VSCS

In the remaining eight patients increasing the prematurity of the test impulse resulted in failure of antegrade conduction *below* the His bundle, in these eight patients the VSCS was more refractory than either the atrium or A V node The H_1 H_2 intervals at which VSCS refractoriness was encountered (i e the ERP of the VSCS) was prolonged and ranged from 410 to 510 msec (average 455 msec) This is in contrast to patients with normal electrocardiograms who typically conduct to the ventricles at comparable H_1 H_2 intervals [10] This extends our previously reported observations[4] and demonstrates that in LBBB the VSCS is abnormally refractory

In patients with LBBB and normal axis it was possible to demonstrate that the refractoriness of

delay The important differences between these two gaps in A V conduction are illustrated in Fig 5

The indirect techniques employed in the present study do not permit precise anatomic localization of the area of maximal refractoriness within the RBB Every premature supraventricular impulse which blocks below the His bundle does so at a gate or site of maximal refractoriness Data in these two patients suggest that this area of maximal refractoriness is located in relative terms distally within the RBB Only conduction delay in a more proximal portion of the RBB allowed A V conduction to resume Whether this means that the area of maximal refractoriness is as distal as shown by microelectrode work in canines or is less distal cannot be proved or disproved by these data

Similarly this study demonstrated that a single fascicle of the human VSCS under certain experimental conditions is capable of marked conduction delay A sufficiently premature test impulse results in marked proximal slowing in the RBB and thus demonstrates that in humans differential refractoriness exists within the RBB with the site of maximal refractoriness located in relative terms distally

Summary

In 15 patients with left bundle branch block (LBBB) atrial (A) His bundle (H) and ventricular (V) electrograms were recorded Successively more premature atrial depolarizations were introduced via a catheter in the right atrium In eight patients the ventricular specialized conducting system (VSCS) was the most refractory portion of the entire atrioventricular conducting system (AVCS) and A V conduction which had been occurring via the right bundle branch (RBB) failed below the His bundle as the effective refractory period (ERP) of the VSCS was reached In two of these eight patients after the ERP of the VSCS was exceeded further shortening of the H H interval (by 40 to 50 msec) resulted in an unexpected resumption of A V conduction but with markedly prolonged H V intervals (160 to 230 msec) This demonstrates that differential refractoriness exists within the RBB of these patients A zone of maximal refractoriness was initially encountered within the RBB when the premature impulse first blocked below the His bundle In relative terms this zone

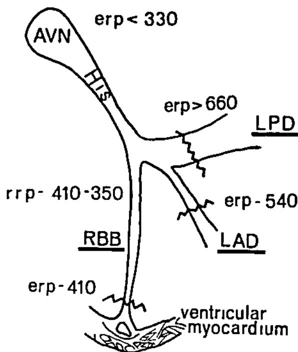


Fig 4 This figure is a schematic representation of the AVCS and proposes an explanation for the gap phenomenon observed in VSCS conduction in two patients Illustrated are the A V node (AVN) His bundle (His) the posterior division (LPD) and anterior division (LAD) of the left bundle branch the right bundle branch (RBB) and the insertion of the distal RBB into a portion of the ventricular myocardium ERP = effective refractory period RRP = relative refractory period All numbers are in milliseconds The figure outlines the sequence of conduction events during the stimulation sequence for patient J T The patient s basic sinus cycle length was 660 msec and at the initiation of the stimulation sequence the ERP of the LPD was exceeded (see text) At an H H interval of 540 msec a leftward shift in mean QRS axis occurred as the ERP of the LAD was reached At this juncture in the stimulation sequence ventricular activation was occurring via the RBB At an H H interval of 410 msec the premature impulse failed to propagate below the His bundle and thus the ERP of the RBB was determined and A V conduction failed With further shortening of the H H interval between 410 and 350 msec conduction delay occurred in an area of the RBB labeled rrp in the diagram which allowed the zone of maximal refractoriness within the RBB to recover excitability and A V conduction to resume This schematic figure should not imply that the anatomic locations for the zones of differing refractoriness are precisely located but rather the figure is intended to indicate relative relationships How far apart in actuality are the zone of maximal refractoriness in the RBB which has an ERP of 410 msec and the zone which with increasing prematurity of H became relatively refractory and caused conduction delay between H H intervals of 410 350 msec was not demonstrated by the techniques employed in the study The ERP of the AVN measured as an A A interval was less than 330 msec because the stimulation sequence ended with atrial and not A V nodal refractoriness

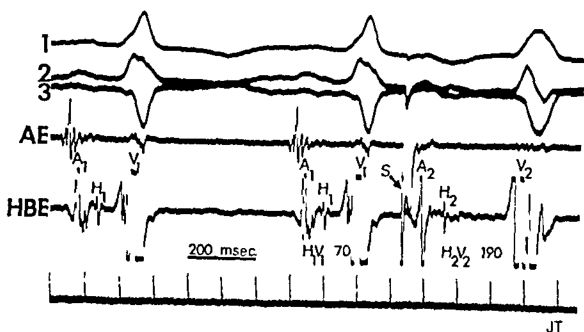


Fig 3 This figure illustrates in detail the prolonged HV intervals noted after the resumption of A V conduction It shows ECG Leads 1 2 and 3 an atrial electrogram (AE) and His bundle electrogram (HBE) Time markers at 100 msec intervals are shown Atrial (A) His bundle (H) and ventricular (V) depolarizations are labeled as in prior figures S represents the stimulus artifact At this H H interval ventricular conduction has resumed but with a markedly prolonged H V, time of 190 msec A leftward shift in axis is noted in the premature ventricular complex in ECG Lead 2

Recently, an experimental technique employing multiple microelectrode recordings from single isolated fascicles of canine VSCS demonstrated that action potential duration and local refractoriness both increase as measurements are made more peripherally [1] A site located distally in the VSCS and termed the gate was shown to be the site of maximal action potential duration and refractoriness The 'gate determines whether a premature impulse once it has entered the VSCS will propagate to the muscle beyond

By employing the extra stimulus method during cardiac catheterization we sought to determine whether distal segments were more refractory than proximal ones in a single fascicle of the VSCS The patient with LBBB seemed an ideal experimental model for these investigations As detailed in earlier studies[4] at $H_1 H_2$ intervals slightly in excess of the ERP of the VSCS, ventricular depolarization is occurring via the RBB Thus, in patients with LBB under certain experimental conditions refractoriness of a single fascicle of the VSCS (i e, the RBB) may be analyzed

In two of fifteen patients with LBBB, as $H_1 H_2$ intervals were shortened, the ERP of the RBB was exceeded and conduction failed at that area of the RBB which was most refractory With further *shortening* of the $H_1 H_2$ interval sufficient conduction delay of the premature impulse within a more proximal area of the RBB allowed conducting tissues at the zone of maximal refractoriness to recover excitability and ventricular conduction to resume Refractoriness at the site of proximal delay was less than at the distal site, since conduction delay of the premature impulse not blockade, occurred at $H_1 H_2$ intervals shorter than the ERP of the RBB itself The extremely long H V intervals occurring after conduction resumed demonstrate that proximal delay was responsible for the resumption of A V conduction via the RBB This explanation is outlined schematically in Fig 4

A recent report employing a similar methodology[11] described a gap in A V conduction which occurred when, after the ERP of the VSCS has been exceeded A V conduction resumed because of conduction delay within the A V node Seven patients were reported two of whom had LBBB and five of whom had normal electrocardiograms In these patients A V nodal delay resulted in *lengthening* $H_1 H_2$ intervals which permitted recovery of the VSCS In our two patients however $H_1 H_2$ intervals continued to *shorten* as test impulses were made more premature The $H_1 H_2$ shortening observed at the time of resumption of A V conduction in our two patients excludes the A V node as the site of conduction

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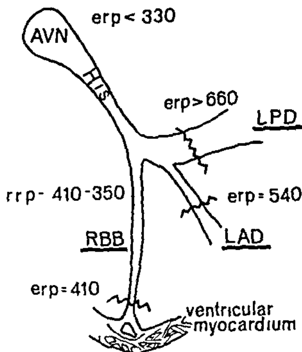


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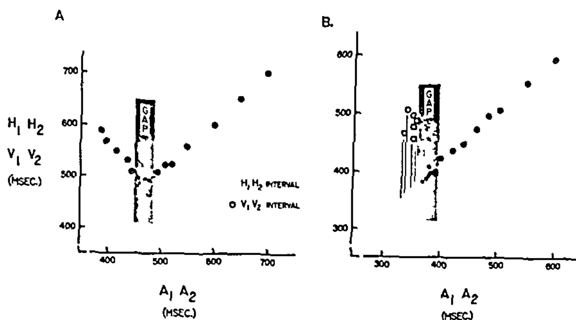


Fig 5 This figure illustrates in graphic form the differences between the gap in AVCS conduction dependent upon AV nodal delay and the gap dependent upon conduction delay within the VSCS In both Panel *A* and Panel *B* H H and V V, intervals are plotted as a function of A A intervals The symbols used are shown in the lower right hand corner of Panel *A* The shaded area labeled gap in both panels is the span of A A intervals during which A V conduction failed below the bundle of His before resuming as the A A interval was further shortened *Panel A adapted after the work of Wit et al shows that as the A A_2 interval is shortened both the* H H and V V intervals shorten as well until an H H was reached at which the ERP of the VSCS was exceeded (~510 msec) As the A A interval was further shortened for a span of 40 msec impulses blocked below the His bundle When conduction resumed at an A A interval of 440 msec it was because A V nodal conduction delay *had increased the H H interval to a value greater than the FRP of the VSCS* As A A continued to shorten the H H and V V intervals both progressively lengthened until the stimulation sequence ended *Panel B* from patient J T shows that as A A was shortened the H H_2 and V V intervals shortened until the ERP of the VSCS was reached at an H H interval of 410 msec The 40 msec interval (stated now in terms of A A intervals) during which conduction of the premature beat failed below the His is shown as in panel *A* When conduction resumed at an A A interval of 340 msec note that unlike panel *A* the H H and V V intervals have diverged because the H V interval is not the same as it was prior to the gap The vertical lines between the His bundle and ventricular symbols represent the prolonged H V intervals for each conducted beat As A A continues to shorten the H H shortens as well until the atrium is refractory Although both gaps can be diagrammed in terms of an A A span of non conducted test impulses the important difference is that the gap in panel *A* is dependent upon A V nodal delay (as evidenced by the lengthening H H intervals) while in panel *B* the gap is dependent upon conduction delay within the VSCS as evidenced by prolongation of the H V time

was distal to a more proximal area of the RBB where with further shortening of the H_1 H_2 interval sufficient conduction delay occurred to permit recovery of excitability distally and the resumption of A V conduction

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Clinical pathologic conference

A 1952 clinicopathological conference with Dr Paul Wood at the National Heart Hospital in London

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It was my responsibility for over 20 years to organize all clinicopathological conferences at the National Heart Hospital my necropsy diagnosis was a secret closely guarded from the Chairman who was one of the Senior Physicians (Sir John Parkinson Dr Maurice Campbell Dr Evan Bedford Dr Paul Wood Dr William Evans Dr Graham Hayward Dr Wallace Brigden Dr Audrey Leatham Dr Lawson McDonald Dr Richard Emanuel) or Surgeons (Sir Thomas Holmes Sellors Mr Donald Ross Mr Keith Ross)

The present conference took place on June 20 1952 in the high ceilinged lecture hall of the old 50 bed hospital which could seat about 80 persons Nearly always these affairs attracted a full attendance of resident staff postgraduates and visiting cardiologists from overseas never more attentive and expectant than when Paul Wood was presiding Two course postgraduates would be detailed to present the clinical findings this usually provided the highlights of the meeting Dr Paul Wood seized on every vague utterance from a nervous presenter with ruthless probing but to my knowledge he never aroused resentment because of the kindness behind his criticism which often ended with a burst of laughter and because of the clarity with which he expounded the point which had aroused his intervention Nevertheless all of us were on our toes throughout the hour or so fascinated by a brilliant analysis of the paper patient No other form of teaching can instill in the pathologist such respect for his colleagues and humility in his necropsy dénouement

The topic of this conference provides as much speculative discussion today as it did in 1952 Moreover it is unlikely that investigatory procedures now current would have helped to elucidate such a case beyond the conclusions reached at this conference it is also debatable whether modern therapy could have improved the outcome

Clinical picture

History The patient was a youth of 18 years who had enjoyed normal health until 7 months before his first admission to hospital when he started to become unduly breathless on exertion The amount of exercise which distressed him became progressively less and within one month even walking for a few minutes proved difficult During this time he suffered lassitude and exhaustion central chest pain unrelated to exertion to respiration or to feeding and cough which produced half a cupful of yellowish brown sputum daily All symptoms persisted until admission Although the cough became less productive within a fortnight the sputum contained flecks of dark blood several times daily In the 3 weeks before admission ankle swelling appeared during the day and breathlessness occurred in bed at night The patient lost weight in the recent 2 months but at no time was there any fever

Past history No previous illness was recalled

Family history This was obtained from an elder sister

The patient s *father* 57 years of age and two paternal uncles were alive and well his *mother* 56 years of age had a brain tumor but a maternal aunt and an uncle were well

Two *sisters* were alive and well the elder 31 years of age suffered from migraine and fainting

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but electrocardiography and radioscopy disclosed no abnormality—neither in her nor in her 6 year old son The younger sister, 21 years of age, suffered nothing other than ill temper

All four of the patient's *brothers* were dead The youngest died at 6 months, possibly from meningitis Another died suddenly and myster iously at 6 years A third brother died at 14 years from pneumonia he was thought to have had diphtheria or rheumatic fever at 6 years The fourth oldest brother died at 19 years (3 days before the third brother and 10 years before our patient) while serving in the Royal Air Force in 1941 from a fulminating illness lasting only 4 days diagnosed as acute influenzal broncho pneumonia and toxic myocarditis in the R A F Hospital, necropsy disclosed pulmonary edema, clear pleural and pericardial effusions, cardiac dilatation without lesion of the valves endocar dium myocardium or coronary arteries, and a nutmeg liver Histological findings in the heart and other organs were not available

First admission to hospital (for 2 weeks) This was to an R A F Hospital (not the one in which his brother had died 10 years previously) He was afebrile but examination disclosed pericardial effusion pericardial tap yielded 300 ml of sterile blood stained fluid The blood leukocyte count was 9 900 per cubic millimeter erythrocyte sedi mentation rate 3 mm per hour and Mantoux test negative His condition did not improve in 2 weeks with the paracentesis supplemented by digitalis sodium salicylate and cortisone therapy so transfer was arranged

Transfer to the National Heart Hospital The patient was admitted under Drs Paul Wood and Aubrey Leatham

The patient was pale and dyspneic at rest The jugular venous pressure was 6 cm at 45 degrees the main wave being systolic The liver was palpable two fingerbreadths below the costal margin and there was massive edema extending from ankles to upper abdomen with some ascites There was dullness at the left lung base with diminished breath sounds coarse crepitations were detected at both lung bases Cardiovascular examination revealed a regular pulse of 90 per minute, of small volume and paradoxical, the blood pressure was 100/? Diffuse precordial pulsation was visible in the fourth and fifth left intercostal spaces and cardiac dullness extended to the midclavicular line in the third interspace with the patient recumbent at 45 degrees Auscul tation disclosed a loud apical third heart sound, an auricular sound between the cardiac apex and lower sternum and a soft high pitched systolic murmur at all areas, there was also a friction sound to the left of the lower sternum No other abnormal signs were detected

Investigations

Urine trace of albumin

Hemoglobin 12 6 Gm /100 ml

Leukocyte count 18 000 cu mm (81 per cent polymorphonuclear leukocytes

Erythrocyte sedimentation rate 6 mm per hour

Wassermann reaction negative

Sputum no tubercle bacilli

Mantoux test negative at 1 in 1,000

Electrocardiogram partial left bundle branch block

Chest x ray marked generalized cardiac enlargement No pulmonary lesion or pleural effusion

Pericardial tap yielded sterile heavily blood stained fluid Microscopy culture and guinea pig inoculation yielded no evidence of tuberculosis

Treatment and progress The basis of treat ment was bedrest on a salt free diet, Neptal (a parenteral diuretic containing mercuramide and theophylline) and streptomycin This induced a good diuresis with lessening of edema but the patient remained orthopneic weak listless and wretched with anorexia and vomiting Pericardial tap on day 22 yielded straw colored fluid The streptomycin was stopped on day 24 because of vertigo and vomiting on this day thrombosis of the left axillary vein occurred From now on progress was downhill edema recurred and proved so intractable that acupuncture (multiple stab incisions in the legs) was resorted to this yielded 25 pints (14 L) of fluid during 5 days reduced greatly the edema and the jugular venous pressure and improved the strength of the heart beat Nevertheless wasting extreme weakness and mental deterioration progressed to death on day 35 At no time was there any fever Although the pulse remained weak and paradoxical its rate remained at 70 to 90 per minute almost through out

Clinical diagnosis This was recurrent pericar dial effusion of undetermined cause the possibil ities discussed were tuberculosis rheumatism neoplasm or a primary idiopathic type of effu



Fig 1 Dilated left ventricle with mural thrombus valves normal

sion Dr Wood favored a tuberculous origin although he was obviously not content with his diagnosis because of the inconclusive evidence

Necropsy findings

The youth was much emaciated but both legs were still edematous from the knees downward and showed acupuncture incisions There was a palpable ropelike mass in the left axilla

Cardiovascular system The *pericardium* was dry and free from adhesions and showed several paracentesis marks The *heart* weighed 560 grams and showed generalized dilatation Mural thrombus lined the apex of the left ventricle (Fig 1) and there was another clot on the anterior wall The cut surface of this chamber was up to 1 cm thick and showed streaky whitish areas The other chambers were dilated but otherwise normal There was no lesion of the valves and the aorta and coronary arteries were normal and free from atheroma The ductus and foramen ovale were both closed The left subclavian axillary vein was occluded completely by organizing thrombus

Histology This revealed widespread mild lymphocytic infiltration of the epicardium (Fig 2) and widespread myocardial replacement fibrosis mainly in the left ventricle (Figs 3 and 4) a few lymphocytes were scattered in the right ventricle and there was an occasional focus of hemorrhage (Fig 5) The endomyocardium beneath the mural thrombus showed no lesion (Fig 6)



Fig 2 Epicardium of left ventricle lymphocytic infiltration (Hematoxylin van Gieson ×90)

Respiratory system The left *pleural cavity* contained 250 ml of blood stained fluid and the right cavity 50 ml of clear yellow fluid there were no adhesions on either side The *lungs* showed edema and congestion especially at their bases with an infarct on the right side Histology revealed scattered foci of acute pneumonitis

Other findings The *peritoneum* was almost dry and was free from adhesions The *liver* weighed 1300 grams and showed a generalized nutmeg pattern The right *kidney* weighed 150 grams and the left 170 grams and the capsules stripped readily histology showed some degeneration of the proximal tubules The *spleen* weighed 180 grams and was firm and congested

Necropsy diagnosis (1951) Idiopathic fibrosis of the myocardium possibly the result of healed myocarditis of Fiedler[1] type This diagnosis was made several years before Brigden[2] introduced



Fig 3 Left ventricle fibrosis (Hematoxylin van Gieson ×90)

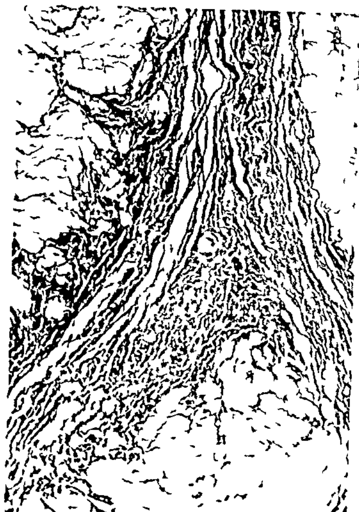


Fig 4 Left ventricle fibrosis (Hematoxylin van Gieson ×90)

the term cardiomyopathy for noncoronary heart disease The description today would be "familial idiopathic fibrotic cardiomyopathy

Discussion

The patient died in 1951 and the conference took place in 1952, many years before the idea of idiopathic cardiomyopathy had become general although cardiologists throughout the world were well acquainted with cases of heart failure without obvious cause Thus in the present case there was no abnormality of the valves or coronary arteries congenital or acquired Uncommon diseases such as systemic lupus erythematosus, scleroderma, and beriberi were excluded The Uganda form of endomyocardial fibrosis then being publicized by Dr J N P Davies and his colleagues—their main papers appeared in 1954 (e g Williams Ball and Davies[3])—was simulated by the apical thrombosis, but excluded on other grounds, such as the absence of endocardial fibrosis creeping over the atrioventricular valves from the apices of the ventricles Hypertrophic cardiomyopathy (Teare s[4] 'asymmetrical hypertrophy 1958 now called idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy etc) was also excluded anyway it was then virtually unrecognized although I had encountered one typical example in 1951 in a youth of 19 years who died suddenly it was presented to me by Prof D M Pryce of St Mary s Hospital in London

The striking feature of the case was the tragic family history all four of the patient s brothers had died before him This case more than any other in my experience sowed the idea that cardiac fibrosis and failure might appear many years after recovery from some infective illness which had caused myocarditis Gore and Saphir[5] in their classical survey of 1 402 cases had demonstrated that the cause might be viral rickettsial bacterial protozoal or metazoal Analysis of the family history, incomplete though it was suggested that at least three and possibly *four of the*



Fig 5 Left ventricle focal hemorrhage (Hematoxylin van Gieson ×90)

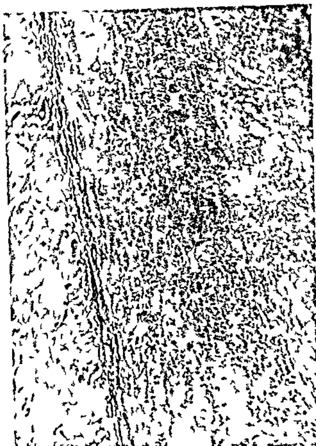


Fig 6 Left ventricle organizing endocardial thrombus (Hematoxylin van Gieson ×90)

five brothers might have suffered an infective disease possibly viral affecting the family

Since 1952 I have encountered personally only one authentic example supporting the postmyocarditic origin of cardiac fibrosis This was in a father who died of florid myocarditis and his son who died of myocardial fibrosis 18 years later I performed both necropsies This illustrates the almost insurmountable difficulty of proving the theory namely the lapse of time between infection and heart failure—the latent period—even assuming that reliable clinical and pathological proof is available in every fatal case Careful epidemiological records of all cases of electrocardiographic" myocarditis might help to establish the theory more firmly Nevertheless I consider that idiopathic myocardial fibrosis is never without cause and that this cause is most likely to be myocarditis unrecognized at the time or long since forgotten

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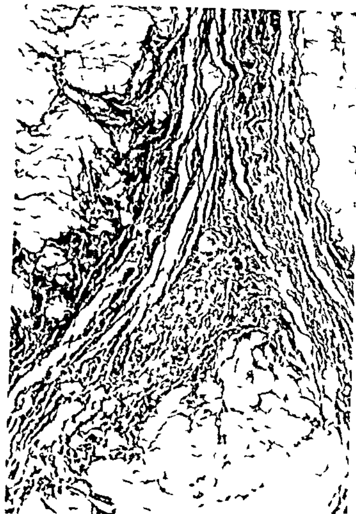


Fig 4 Left ventricle fibrosis (Hematoxylin van Gieson ×90)

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Discussion

The patient died in 1951 and the conference took place in 1952 many years before the idea of idiopathic cardiomyopathy had become general, although cardiologists throughout the world were well acquainted with cases of heart failure without obvious cause Thus in the present case, there was no abnormality of the valves or coronary arteries congenital or acquired Uncommon diseases such as systemic lupus erythematosus scleroderma, and beriberi were excluded The Uganda form of endomyocardial fibrosis then being publicized by Dr J N P Davies and his colleagues–their main papers appeared in 1954 (e g Williams, Ball and Davies[3])–was simulated by the apical thrombosis, but excluded on other grounds, such as the absence of endocardial fibrosis creeping over the atrioventricular valves from the apices of the ventricles Hypertrophic cardiomyopathy (Teare s[4] 'asymmetrical hypertrophy 1958 now called idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy etc) was also excluded, anyway it was then virtually unrecognized although I had encountered one typical example in 1951 in a youth of 19 years who died suddenly it was presented to me by Prof D M Pryce of St Mary s Hospital in London

The striking feature of the case was the tragic family history all four of the patient s brothers had died before him This case more than any other in my experience sowed the idea that cardiac fibrosis and failure might appear many years after recovery from some infective illness which had caused myocarditis Gore and Saphir[5] in their classical survey of 1 402 cases had demonstrated that the cause might be viral rickettsial bacterial protozoal or metazoal Analysis of the family history incomplete though it was suggested that at least three and possibly four of the



Fig 5 Left ventricle focal hemorrhage (Hematoxylin van Gieson ×90)

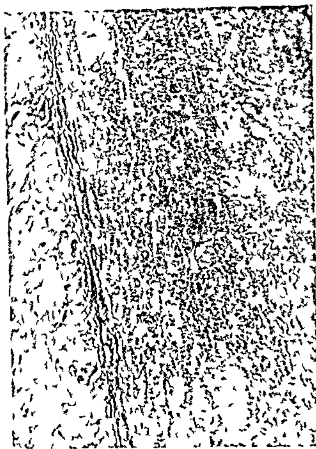


Fig 6 Left ventricle organizing endocardial thrombus. (Hematoxylin van Gieson ×90)

five brothers might have suffered an infective disease possibly viral affecting the family

Since 1952 I have encountered personally only one authentic example supporting the postmyocarditic origin of cardiac fibrosis This was in a father who died of florid myocarditis and his son who died of myocardial fibrosis 18 years later I performed both necropsies This illustrates the almost insurmountable difficulty of proving the theory namely the lapse of time between infection and heart failure—the latent period—even assuming that reliable clinical and pathological proof is available in every fatal case Careful epidemiological records of all cases of electrocardiographic myocarditis might help to establish the theory more firmly Nevertheless I consider that idiopathic myocardial fibrosis is never without cause and that this cause is most likely to be myocarditis unrecognized at the time or long since forgotten

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Factors controlling impulse transmission with special reference to A-V conduction

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Various atrioventricular (A V) conduction disturbances form one major category of cardiac arrhythmias, and have been the subject of innumerable reports in clinical and experimental cardiology In these studies, the electrocardiogram for many decades remained the most widely used and perhaps the only reliable method of study, although the earliest observations on second degree A V block by Wenckebach (1899) were made with the recordings of radial arterial and jugular venous pulses[1] Despite the limitations of electrocardiography which enables us to record only the atrial and ventricular electrical events precise measurements of various intervals and astute theoretical deductions have proved quite successful in elucidating many complex aspects of A V conduction [6] However, it is after the application of the microelectrode techniques in cardiac electrophysiology in the late 1950 s that our understanding of the phenomenon of impulse transmission at the cellular level has been achieved An earlier review by Hoffman[7] has identified the complex nature of A V transmission but new information has expanded our knowledge considerably in the last ten years Furthermore the introduction of His bundle electrography into clinical cardiology has greatly increased the momentum in the study of atrioventricular conduction

Hence, in this communication various factors which control the propagation of cardiac impulses in general (Table I) will be reviewed first and some of the peculiarities of A V conduction discussed

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Factors controlling impulse transmission

Primary determinants of conductivity

Physiologic factors As shown in Table I, two major factors to be discussed here are (1) effectiveness of stimuli produced by depolarization of the upstream fibers, and (2) excitability of the responding, downstream fibers Regarding the former it has been established that the action potential amplitude and the rate of phase 0 depolarization are the two major determinants of the effectiveness of a stimulus as well as the conduction velocity between contiguous fibers[8] Thus an action potential with a greater amplitude and a more rapid rate of phase 0 depolarization is more effective as a stimulus and is accompanied by a higher conduction velocity whereas conduction is much slower in fibers showing decreased rate and amplitude of phase 0[7,13]

These action potential characteristics vary from one group of fibers to another and the resultant dissimilarities of conductivity between different portions of the A V conducting system are discussed later in greater detail Furthermore even in a given fiber type the action potential characteristics are dependent upon several factors Most importantly, the higher (the more negative) the level of membrane potential at the onset of phase 0 the greater the maximal rate of depolarization (dV/dt) and vice versa[14,1] This relationship was first demonstrated by Weidmann[14,15] and is usually expressed by a membrane responsiveness curve (Fig 1)

Variations in the membrane potential as shown in Fig 1 can result from many mechanisms For instance, the cell membrane may be hypopolarized (partially depolarized) by factors such as anoxia[18,19] high potassium concentration,[8,] and excessive administration of quinidine or other antiarrhythmic agents[1] resulting in a reduced upstroke velocity of phase 0 Contrariwise factors

Table 1 Factors controlling impulse transmission

I Primary determinants of conductivity
A. Physiologic factors
1 Effectiveness of stimuli produced by depolarization of upstream fibers
2 Excitability of responding downstream fibers
3 Temporal fluctuation of 1 or 2
B Anatomic factors
1 Fiber diameter
2 Geometric arrangement of fibers
II Abnormal conduction phenomena resulting from alterations in the primary determinants of conductivity
A Decremental conduction
B Inhomogeneous conduction
C Conduction delay and block
D Unidirectional block
E Re-entry
III Abnormal conduction phenomena secondarily affecting conductivity
A Conduction delay and block
1 Effects of conduction delay on the action potential duration (prolongation)
2 Effects of conduction block on the action potential duration of fibers proximal to the site of propagation failure (shortening)
3 Effects of conduction block on the action potential duration of fibers distal to the site of propagation failure (prolongation)
4 Effects of conduction delay or block on excitability of the downstream fibers
5 Conduction delay or block causing impulse formation in the downstream fibers
B Re entry
1 Collision of re entrant impulse with the more slowly advancing antegrade wave of excitation resulting in cancellation of both wave fronts
2 Further disorganization of the excitation front (increased inhomogeneity) in subsequent impulse transmission
3 Reorganization of the excitation front (decreased inhomogeneity) in subsequent impulse transmission

which hyperpolarize the membrane like low extracellular potassium concentration or high magnesium concentration [6] may increase the rate of phase 0 depolarization and the conduction velocity on this basis Thus various pathophysiologic changes could affect the level of the resting membrane potential and the conductivity in the tissues involved

On the other hand depending on the interval between two successive stimuli depolarization may start in a fiber before it is fully repolarized from a preceding excitation Such premature discharge during the relative refractory period is

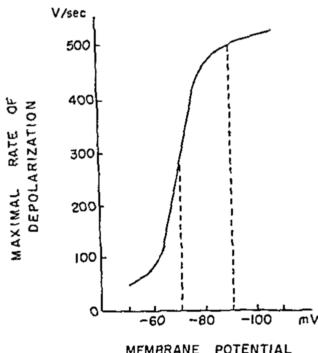


Fig 1 Typical membrane responsiveness curve It is seen that the maximal rate of phase 0 depolarization is approximately 500 volts per second at a membrane potential of −90 mV while it is reduced to less than 300 volts per second at a lower membrane potential of −70 mV

associated with varying degrees of reduction in the rate as well as the amplitude of phase 0 [8] and may even prove to be ineffective in exciting the adjoining fibers Another mechanism altering the membrane potential at the onset of excitation is the development of slow diastolic depolarization in automatic fibers of the specialized conducting system Since the loss of membrane potential due to phase 4 depolarization proceeds with time this mechanism for depression of conductivity is more likely to occur after a prolonged electrical diastole Thus the interval between two impulses could indirectly influence the efficacy of a stimulus either as a result of incomplete repolarization or of progression of phase 4 depolarization

In addition to the level of membrane potential at the onset of excitation as discussed above the level of threshold potential also plays a role in determining the rate of phase 0 depolarization Although this factor seems to have received less attention than the membrane potential its importance would be readily apparent when one recalls the fact that depolarization becomes all or none only when the membrane attains the threshold potential [8] Furthermore it has been shown

that the level of the threshold potential becomes lower (less negative) with the development of diastolic depolarization[17] Hence, in fibers showing significant automaticity, conduction velocity can be markedly decreased by the lowering of the membrane resting potential as well as the threshold potential This mechanism may be responsible for the production of exit block from an ectopic pacemaker[21] and for the so called protection block around a parasystolic focus

Recently, increasing attention is being paid to the presence of a fast and a slow component in cardiac action potentials According to this theory, initial rapid upstroke (phase 0) of the action potential results from the fast inward sodium current while the slow component responsible for the plateau phase is dependent, at least in part upon a calcium current[24 27] That these components represent two qualitatively different processes is illustrated by several observations such as (1) the fast sodium current is rapidly activated and inactivated while the slow current is activated and inactivated more slowly, (2) the former is dependent on extracellular sodium concentration and is abolished by tetrodotoxin whereas the latter is dependent upon extracellular calcium concentration, is abolished by manganese, verapamil, and lanthanum but insensitive to tetrodotoxin, and (3) the fast current is inactivated by partial depolarization, while the slow current is activated at a less negative threshold potential than that of the fast component[28 29] Then, it follows that when cardiac tissues are markedly depressed by some of the factors mentioned above (e g sustained depolarization) the observed reduction in the rate of phase 0 depolarization and the conduction velocity may be a result of partial (or total) inactivation of the fast sodium current with the slow current becoming predominantly responsible for the slowly rising action potential

Furthermore, recent experimental studies appear to suggest that the action potentials from the sinoatrial node and the N region of the A V node which show inherently slow rate of phase 0 depolarization, are mainly dependent upon this slow channel[28] A linear relationship between external calcium concentration and the action potential amplitude of the A V nodal cells as observed by Matsuda[30] and the insensitivity of intranodal conduction to tetrodotoxin reported earlier by Watanabe[11] are well in keeping with this concept

On the other hand, the second major determinant of conductivity, or the excitability of downstream fibers, is dependent upon several factors (Table I) First, the diastolic threshold of stimulation is defined as the minimal strength of stimuli (or amount of depolarizing current) capable of producing a full depolarization of a tissue during its electrical diastole[8] Thus a high diastolic threshold implies a lowered excitability, and a low diastolic threshold, an increased excitability One possible reason for an increase in the current requirement is a greater distance between the membrane resting potential and the threshold potential, although it is likely that other mechanisms are also involved When the diastolic threshold in a tissue is elevated for some reason impulses which have previously been effective in exciting the tissue may now fail to bring the membrane resting potential to the level of the threshold potential Such stimulus is called subthreshold, and will result in a conduction block

Ordinarily, the excitability of cardiac fibers remains stable during phase 4 Contrariwise the excitability undergoes a sequential change with the onset of activation and throughout electrical systole[8 3] Once a cell is fully depolarized in phase 0 the cell membrane becomes refractory to however strong a stimulus throughout the entire plateau phase (phase 2) and part of phase 3 This period is called the effective refractory period of a tissue and an impulse arriving during this phase of cardiac cycle fails to be propagated At some point during phase 3 of repolarization the effective refractory period ends and the relative refractory period begins During the latter the excitability is higher and the cell responds only to a stronger stimulus than during phase 4 As has been discussed above, graded responses produced during this period show varying degrees of impaired conduction

Since the duration of the effective refractory period shows a positive correlation with the action potential duration and the action potential duration is, in turn, a function of the cycle length it can be generalized that a longer cycle length (or a slower heart rate) is associated with a longer action potential duration and a more prolonged refractory period and vice versa[8 33] However the above correlation between the process of repolarization and the recovery of excitability is not quantitatively constant More specifically, the membrane potential attained at the end of the

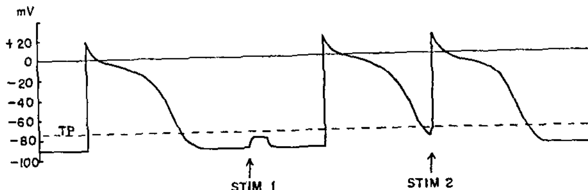


Fig 2 A possible mechanism for the supernormal period of excitation A weak stimulating current (STIM 1) fails to bring the membrane resting potential to the threshold potential (TP) during phase 4 whereas a similar ordinarily subthreshold stimulus (STIM 2) may successfully reduce the membrane potential to TP when repolarization has proceeded beyond TP but short of the resting potential (Reproduced from Watanabe Y Arrhythmias Electrophysiologic and Clinical Aspects Tokyo 1973 Bunkodo)

effective refractory period may vary in different fiber types and even in the same single fiber under various pathophysiologic conditions [6] This implies that the earliest possible response at the termination of the effective refractory period may in some fibers start from a more negative membrane potential and show a relatively normal conductivity but in others start from a lower membrane potential and show a markedly depressed conductivity The effects of certain antiarrhythmic agents have been attributed partly to alterations in this relationship [6 3 3]

The phenomenon of supernormality and the Wedensky effect deserve comment Mainly in the specialized conducting system a brief period with enhanced excitability is often seen toward the end of the relative refractory period This period is termed the supernormal phase of excitability [3] A possible explanation for this phenomenon is that when repolarization has progressed beyond the threshold potential but has not yet attained the level of the resting potential the membrane may be brought back to its threshold potential with a weaker stimulus than during phase 4 When the strength of available impulses is barely sufficient to depolarize a cardiac fiber to its thres hold potential a propagated response may be produced only during the supernormal period and in no other phases of cardiac excitability (Fig 2)

On the other hand the Wedensky effect is defined as a temporary increase in excitability following a supramaximal stimulation For instance weak stimuli from an electronic pace maker that are ordinarily subthreshold may be come effective to excite the ventricular muscle for certain period of time after a strong electrical stimulation has been applied [37] One difference be tween the Wedensky effect and the supernormal excitability is that the duration of the former is often much longer than that of the latter Both of these phenomena have been invoked by several investigators to explain the genesis of so called coupled premature systoles [36 3]

A somewhat different variety of alteration in excitability of the downstream fibers concerns with the effect of premature depolarization in these fibers When the tissue ahead of an advanc ing excitation front is prematurely discharged by a second impulse a state of refractoriness is produced which affects forward propagation of the initial impulse Indeed collision of the two (forward and retrograde) wavefronts would result in a cancellation of both impulses This type of conduction block has been observed to occur experimentally [39] Even in the absence of an actual collision of impulses a refractory tissue remaining in the wake of previous depolarization could cause varying degrees of conduction delay or even block

In contrast such premature discharge of the downstream fibers by another impulse may some times affect their excitability in a different manner For instance a premature atrial impulse which ordinarily is blocked by a prolonged refrac tory period of the A V junctional tissue following the preceding forward conduction may be permitted to traverse this region when a prema ture depolarization of this tissue by a retrograde impulse caused an early recovery of excitability

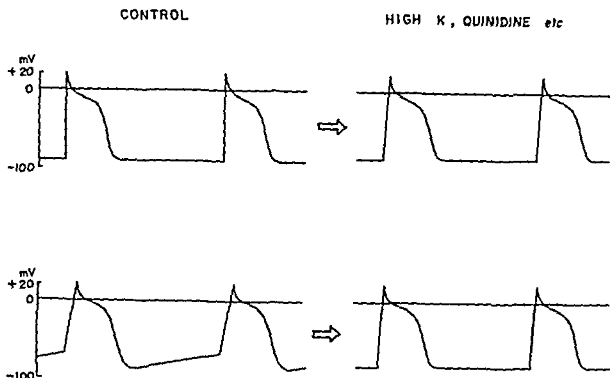


Fig 3 Contrasting effects of certain antiarrhythmic agents on the rate of phase 0 depolarization (and conduction velocity) in His Purkinje fibers in the absence and in the presence of significant diastolic depolarization At top high potassium concentration or quinidine may reduce the upstroke velocity of the action potential either by shifting the *membrane responsiveness curve or by partially depolarizing the fibers.* At bottom these same factors suppress automaticity and secondarily improve conduction by increasing the membrane potential at the end of phase 4 (Reproduced from Watanabe Y Clinical pharmacology of cardiovascular drugs Antiarrhythmic agents *In* Ito Y editor Diagnosis and Management of Circulatory Disturbances. Tokyo 1974 Kimbara Publishing Company)

This mechanism has been termed 'peeling back of the refractory barrier' and advocated by some investigators as the cause of one type of super normal A V conduction[40,41] However this con cept cannot explain similar apparent facilitation of forward conduction by appropriately timed retrograde impulses in the presence of a regular atrial rhythm and high grade A V block, as reported by Pick Langendorf and Katz (Fig 3 of Ref 5) Hence, certain reservations must be made before such peeling back of the refractory barrier is accepted as a universal explanation for these conduction phenomena

The two physiologic factors discussed above or (1) the effectiveness of stimuli produced by depo larization of the upstream fibers and (2) the excitability of the responding downstream fibers do not necessarily remain constant for a prolonged period of time, and slight fluctuations of conductivity in a tissue are considered to be the rule rather than the exception Under normal physiologic conditions, such temporal fluctua tions of conductivity would not significantly affect transmission of impulses Contrariwise in depressed tissues having a narrow margin of safety, a slight fluctuation from one beat to the next may well determine the success or failure of propagation in all or none fashion[42] It is possible that this mechanism operates in some cases of A V conduction block, particularly of the so called Mobitz Type II variety

Anatomic factors At least two factors deserve consideration in this category, or *(1) fiber* diameter and (2) geometric arrangement of fibers Regarding the fiber diameter, the so called cable property of fibers dictates that the larger the diameter of a fiber the easier and the more rapid is the transmission of impulses[43] This property undoubtedly provides one explanation for the greater conduction velocity in Purkinje fibers than in ordinary ventricular or atrial muscle fibers[8]

The second factor, or geometric arrangement of fibers deals with the following several varieties First it has been shown that the conduction velocity is greater when an impulse travels a fiber

in the longitudinal direction than in the transverse fashion.[44] This would affect the spread of excitation in a large mass of cardiac fibers. On the other hand, coalescence (or convergence) of several smaller fibers into a single larger fiber could cause summation of impulses, while branching (ramification) of one fiber into many smaller ones may result in fractionation of the wave front. Propagation is considered to occur more easily in the former than in the latter condition. The same argument applies at any junction of two tissues with dissimilar masses, e.g., the site of insertion of one peripheral Purkinje fiber into a group of ventricular muscle fibers. Indeed, experimental studies using two portions of large atrial tissue connected with a narrow isthmus have shown that failure of transmission occurs much more readily from the isthmus to the larger tissue than in the opposite direction.[5] This finding has been used to explain intermittence of conduction through the accessory A-V pathways like the bundle of Kent.

In addition to these two varieties, discontinuity of fibers (perhaps due to the failure of resorption of fibrous A-V ring) may be regarded as another anatomic factor. Such interruption of fibers would obviously cause failure of propagation. Some cases of congenital complete A-V block have been shown to result from anatomic discontinuity of the specialized conducting system.

Abnormal conduction phenomena resulting from alterations in the primary determinants of conductivity

Decremental conduction. The term decremental conduction can be defined as "a progressive decrease in the effectiveness of a stimulus as well as the magnitude of response along the pathway of conduction, occurring in an anatomically uniform but functionally depressed tissue." When the resting membrane potential is decreased from the normal physiologic level in a given cardiac tissue by various pathophysiologic derangements, the action potential would show a reduced rate and amplitude of phase 0 depolarization, implying a decreased efficacy of the stimulus. Since the neighboring (downstream) fibers would also possess lower membrane potentials as a result of the same pathophysiologic abnormalities, the action potential characteristics may show a progressive deterioration in the course of propagation, i.e., a decrement. Recent studies on the slow inward current during depolarization in depressed tissues and extremely slow conduction resulting from activation of such slow channels[2, 29] may lend further support to the concept of decremental conduction.

In the above definition of decremental conduction, the second half is quite important. For instance, both the amplitude and the rate of phase 0 depolarization become progressively smaller from the atrial fibers to the AN region and from the AN to the N region of the A-V node.[6, 7] However, this should not be considered an example of decremental conduction, since conduction in this case involves anatomically nonuniform tissues and those changes in the action potential merely reflect different physiologic properties in individual fiber types. In other words, these tissues are not abnormally depressed, while functional depression is a prerequisite for decremental conduction. Of course, decremental conduction can and often does develop in the A-V node when its conductivity is abnormally depressed.[19] The lower amplitude and rate of phase 0 depolarization inherent to this tissue would easily set the stage for decrement.

Inhomogenous conduction. When conductivity in individual fibers is depressed and decremental conduction develops to different degrees at a given level of the A-V transmission system, the advancing front of excitation may become irregular and disorganized instead of being smooth and organized. Then this wave front will be less effective in depolarizing the more distal tissues and the propagation more difficult. This type of conduction disturbance has been termed as *inhomogeneous conduction*.[39] Obviously, such inhomogeneity of conductivity is less likely to develop within a narrow bundle or tract in which the fibers are arranged quite compact and in parallel to one another. On the other hand, disorganization of the excitation front would be produced much more readily in the A-V node, where the *fiber diameter* is small as well as variable, and numerous branchings and interconnections of these cells form a complex netlike structure.[5]

Although the above anatomic peculiarities of the A-V node may possibly cause a nonuniform excitation front even under physiologic conditions with numerous collisions of impulses occurring in these interconnecting branches, the irregularities are not marked and conduction proceeds

uneventfully However, when the A V nodal tissue is depressed, disorganization of the excitation front may become sufficiently marked to affect overall conductivity across the node An extreme inhomogeneity could sometimes result in a failure of propagation on one side of the A V node with a slow but successful conduction on the other This condition is known as functional, longitudinal dissociation which could lead to re entry or reciprocation of impulses[39] Thus it may be said that inhomogeneous conduction is a longitudinal (or parallel) expression of decreased conductivity, while decremental conduction is a transverse (or series) expression of depressed conductivity Recent observations appear to suggest that such inhomogeneity could develop in tissues other than the A V node, resulting in re entrant movements[51,52]

It should further be pointed out that decremental conduction would favor the development of inhomogeneous conduction while the latter would tend to aggravate the former, thus often forming a vicious cycle to cause a conduction block

Conduction delay and block Alterations in any one of the primary determinants of conductivity, either alone or in combination with others, could cause a delay or block (failure) of propagation The close interrelationships of the two abnormal conduction phenomena, or decremental conduction and inhomogeneous conduction, in causing delay and block of excitation front have just been discussed In tissues other than the A V node (1) loss of membrane potential either by partial depolarization or by enhanced diastolic depolarization,[13] and (2) the presence of refractory fibers are perhaps the two most common causes of conduction delay and block

Unidirectional block Under certain pathophysiologic conditions a depressed cardiac tissue may transmit impulses only in one direction and not in the other This phenomenon is termed unidirectional block (or unidirectional conduction) Experimental observations of such unidirectional conduction were first made by Schmitt and Erlanger[53] in isolated, compressed strips of cardiac muscle while the concept of unidirectional block has often been invoked in explaining various electrocardiographic findings[54,55] The mechanism for this phenomenon most likely is considered to be dissimilar degrees of decrement depending on the direction of propagation[23] Certain anatomic features of the conducting system allowing summation of impulses in one direction (which facilitates conduction) and causing fractionation of wave front in the other (which interferes with conduction) may well be one possible mechanism[56,57] Unidirectional conduction has been shown to occur within the A V node as well as in the peripheral ramification of the His Purkinje system[3,51,5]

Re entry Re entry of one and the same impulse with re excitation of the initially depolarized fibers has been invoked to explain the genesis of various cardiac arrhythmias[58,60] The prerequisites for re entry are (1) depressed conductivity with unidirectional block, and (2) either the development of functional longitudinal dissociation or the presence of two anatomically separate pathways, showing different degrees of depression[3,61] A re entry movement can occur either involving a relatively large mass of cardiac tissue (macrore entry) or within a small group of fibers (microre entry) Although this distinction may sometimes be difficult (1) circus movement in the presence of Wolff Parkinson White syndrome and (2) reciprocal beating in the A V junction can be considered examples of the former In contrast, a microre entry may be seen in any regions of the cardiac tissue and possibly plays an important role in the genesis of premature systoles, ectopic tachycardias, as well as fibrillation[23,62,63]

Abnormal conduction phenomena secondarily affecting conductivity

Conduction delay and block Delay and failure of conduction as discussed above may show various secondary effects on conductivity Varieties of these secondary effects are listed in Table I

In the presence of a decreased conduction velocity in a portion of cardiac tissue, its delayed depolarization will consequently cause a delay in repolarization and recovery of excitability, even when the duration of action potential as well as refractory period remains unaffected Furthermore recent experimental observations indicate that a slow conduction may actually be associated with a prolonged action potential duration probably due to a slow electrotonic spread from the adjacent fibers[51] Hence in tissues showing a significant conduction delay, the end of their refractory period could be markedly delayed adversely affecting transmission of subsequent impulses through this depressed region It is

conceivable that this mechanism plays some role in producing advanced second degree or high grade A V block particularly when atrial rhythms are rapid

On the other hand both conduction delay and block could affect excitability of the downstream fibers in two ways First extremely slow propagation in the proximal portions of the tissue may afford a longer period of recovery for the more distal regions and improve their conductivity Indeed it has been demonstrated that some early atrial premature impulses fail to reach the ventricles because of the long refractory period in the His Purkinje system while further shortening of the coupling interval may paradoxically result in a successful A V transmission[64] In the latter case the premature impulse travels through the A V node with a much greater delay and arrives at the His Purkinje fibers immediately after expiration of their refractory period The phenomenon of gap in A V conduction represents this variety[5,6] Blockage of an impulse with resultant long pause would obviously have similar effects

Contrariwise conductivity in the downstream fibers may sometimes be depressed due to conduction delay or block in upstream fibers When a significant diastolic depolarization is present in the more distal areas of the conducting system prolongation of the cycle length by delay or block in the proximal region would result in a greater loss of membrane potential and hence reduced rate and amplitude of phase 0 depolarization[1] Conduction velocity in these downstream fibers would then be decreased Aberrant intraventricular conduction of A V junctional escape beats has often been explained on this basis[6]

Failure of propagation in a region of the conducting pathway also affects the action potential duration of both proximal and distal fibers For instance an abnormally short action potential has been observed in the depolarized fibers immediately above the site of block This finding has been attributed to a short circuiting of the repolarizing current to the unexcited fibers beyond the site of conduction failure[6] Although alterations of subsequent conduction due to such abbreviation of action potential duration have not been documented a faster recovery of conductivity may be theoretically expected An increased possibility of re entry into this area of early repolarization has also been suggested[7]

The effects of conduction block on the action potential duration of the more distal fibers are quite opposite For those fibers blockage of one impulse causes a sudden doubling of the cycle length Thus upon arrival of the next propagated impulse the action potential duration as well as the refractory period in these fibers will be prolonged When such prolongation is marked the third impulse may find these fibers still refractory resulting in delay or block Possible role of this mechanism in some instances of second degree or advanced second degree A V block has previously been discussed[2]

Another secondary effect of conduction delay or block involves impulse formation in the downstream fibers When the difference between automaticity of the S A node (primary pacemaker) and that of the A V junctional tissue (latent pacemaker) is small marked conduction delay in the proximal portions of the A V transmission system may lead to an escape of a latent pacemaker A new impulse thus formed would depolarize the downstream fibers and either collide with the oncoming sinus impulse or leave a state of refractoriness This certainly could prevent successful propagation of the S A nodal impulse Block of one impulse with resultant doubling of the cycle length would be accompanied by an even greater chance for such discharge of a subsidiary pacemaker often producing various complex arrhythmias[58,60]

Re entry Re entry of cardiac impulses can secondarily affect conduction (Table I) It is one of the premises of re entry that an impulse which traversed a less depressed portion of the cardiac tissue at a somewhat greater speed would enter the more depressed but still unused region from the distal end[2,5,61] Such a retrograde wave of excitation may sometimes collide with the more slowly advancing orthograde impulse resulting in cancellation of both wavefronts[59] Although strictly speaking this is only an abortive re entry it definitely affects conduction Re entry movement with collision of the two excitation fronts within the A V node was first demonstrated by us using microelectrode techniques[3]

In contrast to the one discussed above the following mechanisms may still be regarded as only theoretical Since depression of conductivity in individual fibers of a re entry circuit could occur in numerous combinations the geometry as well as the extent of travel of the re entrant wavefront may vary from one instance to

uneventfully However, when the A V nodal tissue is depressed, disorganization of the excitation front may become sufficiently marked to affect overall conductivity across the node An extreme inhomogeneity could sometimes result in a failure of propagation on one side of the A V node with a slow but successful conduction on the other This condition is known as functional longitudinal dissociation, which could lead to re entry or reciprocation of impulses[39] Thus, it may be said that inhomogeneous conduction is a longitudinal (or parallel) expression of decreased conductivity, while decremental conduction is a transverse (or series) expression of depressed conductivity Recent observations appear to suggest that such inhomogeneity could develop in tissues other than the A V node resulting in re entrant movements[51,52]

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Abnormal conduction phenomena secondarily affecting conductivity

Conduction delay and block Delay and failure of conduction as discussed above may show various secondary effects on conductivity Varieties of these secondary effects are listed in Table I

In the presence of a decreased conduction velocity in a portion of cardiac tissue, its delayed depolarization will consequently cause a delay in repolarization and recovery of excitability even when the duration of action potential as well as refractory period remains unaffected Furthermore recent experimental observations indicate that a slow conduction may actually be associated with a prolonged action potential duration probably due to a slow electrotonic spread from the adjacent fibers[51] Hence in tissues showing a significant conduction delay, the end of their refractory period could be markedly delayed adversely affecting transmission of subsequent impulses through this depressed region It is

propagation ıs that this system contains numerous automatic fibers[8] The effects of diastolic depolarization in these fibers in decreasing the conduction velocity of supraventricular impulses through the loss of membrane potential [3] have already been discussed On the other hand automaticity with resultant impulse formation may also have an adverse effect on conduction by prematurely discharging the A V junctional tissues and leaving a state of refractoriness [76, 77] whereas it could of course be beneficial in preventing ventricular asystole when the sinus node fails to control the ventricles at an adequate rate [23, 58]

In addition to these static differences various fiber types within the A V transmission system show dynamic alterations i e dissimilar responses to individual pathophysiologic or pharmacologic factors For example several factors including low extracellular potassium concentration cardiac glycosides and generalized anoxia predominantly depress conduction across the A V node while sparing the intra atrial and His Purkinje conduction [72, 80] Contrariwise high potassium concentration diphenylhydantoin and quinidine appear to have opposite effects with predominant depression of intra atrial and His Purkinje transmission [78] There are still other factors which slow conduction in all areas of the specialized conducting system [2] Hence the overall response of the A V transmission system would depend upon the net results of these alterations in individual fiber types

It must also be pointed out that whether significant automaticity is present or not could affect responses of certain specialized fibers to the same physiologic or pharmacologic factors For instance direct membrane effects of quinidine tend to reduce the rate of phase 0 depolarization and conduction velocity mainly through the rightward shift of the membrane responsiveness curve [3, 2] although high concentrations of this drug may also cause partial depolarization which further decreases the upstroke velocity of the action potential [3] These statements hold true with Purkinje fibers not showing significant diastolic depolarization (Fig 3 top) When conductivity in the Purkinje system was initially decreased because of a prominent phase 4 depolarization and the loss of membrane potential suppression of such automaticity by quinidine may result in an increased membrane resting potential and a greater conduction velocity (Fig 3 bottom) an action exactly opposite to the one discussed above[8] Similar arguments can be presented with high potassium concentrations In contrast low potassium concentration could depress conduction by enhancing diastolic depolarization and reducing the membrane potential If however the membrane resting potential was initially low due to the presence of depressing agents like quinidine lowering of the potassium concentration may hyperpolarize the membrane and improve conduction in the His Purkinje system [78, 85]

A brief discussion is in order concerning different types of A V conduction block and their significance Classically second degree atrioventricular block has been divided into two types the one showing blockage of an atrial impulse preceded by progressive prolongation of the A V interval has been referred to as the Wenckebach phenomenon or type 1 block whereas sudden dropping out of a ventricular beat following upon a constant and often normal A V conduction time has been called Mobitz Type II (or simply type 2) A V block [5, 5, 87] Recently attention has been focused to the observation that the level of conduction failure in type 1 block is most commonly within the A V node while that in type 2 block is usually below the A V node or within the His Purkinje system [6, 8, 9] Thus in a majority of cases conducted sinus beats show normal QRS duration in type 1 block and abnormally widened QRS in type 2 block However exceptions to the above rule may be observed as Wenckebach periodicity could occur in any severely depressed tissues including the His Purkinje system[9] or even between contiguous ventricular muscle fibers whereas a Mobitz Type II block may occasionally be associated with normal QRS complexes [60]

Our clinico electrocardiographic studies have revealed that the course and prognosis of chronic A V block are best correlated with the QRS duration [3] More precisely the incidence of major symptoms and cardiac death is higher and the need for electronic pacemaker implantation is greater in cases with wide QRS than in those with normal QRS duration regardless of the degree of block (second degree or high grade) These observations led us to propose a new classification of A V block based on the QRS duration i e second degree or high grade A V block with

Table II Specific considerations on atrioventricular conduction

I	Different fiber types with dissimilar conductivity constituting the A-V transmission system
II	Progressive prolongation of the action potential duration toward the downstream fibers
III	Dissimilar responses of different fiber types to various pathophysiologic and pharmacologic factors
IV	Different responses of specialized fibers in the presence vs in the absence of diastolic depolarization
V	Inherent automaticity affecting conduction either through a loss of membrane potential or through a new impulse formation
VI	Types of A-V conduction block physiologic vs clinical considerations (Types 1 and 2 vs types A and B)

another. Thus, in some cases re-entry of an impulse may further increase nonuniformity of depression and the excitation front of the next impulse becomes more severely disorganized. This will result in greater difficulty of forward conduction and perhaps, a greater chance for re-entry. Second degree block with Wenckebach phenomenon may well be produced by such a sequence of events.[58] Contrariwise, it is possible that certain re-entry movements could produce more uniform conductivity. Then the next orthograde impulse may proceed with a much smoother or better organized excitation front and propagation may become easier. This concept provides a possible explanation for some instances of so-called supernormal A-V conduction.[61] It must be pointed out that either increased disorganization or reorganization of the subsequent wavefront of excitation as discussed above could be produced by any retrograde impulses other than the re-entrant ones. Ectopic impulse formation due to either single or sustained re-entry movement would obviously affect transmission of the sinus impulses.

Specific considerations on atrioventricular conduction

Although the above discussion has already touched upon several aspects of A-V transmission, those conduction phenomena could occur, at least theoretically, in any portions of the cardiac tissue. Since atrioventricular conduction has several specific features which cannot be covered by these general considerations, additional comments as listed in Table II appear warranted.

First, the A-V transmission system consists of different fiber types with dissimilar conductivity. For instance, several studies have indicated that sinus impulses would preferentially utilize the atrial specialized conducting system for their propagation to the A-V node, although the ordinary atrial muscle fibers could also participate in internodal conduction.[9-11] A greater conduction velocity in the atrial specialized fibers than in the atrial muscle has been suggested. It is well known that the speed of propagation is extremely slow within the A-V node, while it is quite rapid in the His-Purkinje system.[8-11]

Furthermore, these fiber types possess dissimilar durations of action potential and refractoriness. Generally speaking, the action potential duration becomes progressively longer toward downstream, or from the atrial fibers to the AN, N, and NH regions of the A-V node,[12] the His bundle, bundle branches, and finally to the peripheral Purkinje fibers.[8-13] Thus the possibility always exists that a premature discharge of upstream fibers immediately after their repolarization may fail to fully depolarize the downstream fibers which are still completely or partially refractory. Especially, the longest action potential duration seen in the Purkinje fibers several millimeters proximal to the Purkinje-ventricular muscle junction has been shown to affect transmission of premature impulses with short coupling intervals in either direction. This has been termed the "gating mechanism"[74] and its role in the formation or termination of ventricular arrhythmias has been advocated by several investigators. Even at the same level of the intraventricular conducting system, localization of fibers seems to affect their repolarization as the presence of longer action potential duration in the right than the left bundle branch has been suggested.[75] Such slower recovery of excitability in the right bundle most likely explains the common occurrence of aberration with right bundle branch block configuration in early atrial premature systoles.[60] An alternative explanation is that, even when the reduction in conduction velocity of a premature response is the same in both bundle branches, propagation takes longer in the right bundle having a longer course before reaching the ventricular muscle than the left bundle, thus producing an apparent bundle branch block pattern.

The third inherent property of the A-V conducting system as compared to local cell-to-cell

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normal QRS is termed type A, and those with an abnormally wide QRS are called *type B*.[90, 91]

Ideally, the site of propagation failure should be indicated in each case of A-V conduction block since it is the major determinant of the clinical significance of heart block, and since identification of the site of block is now easier with the use of His bundle electrography. However, recording of His bundle electrograms in every single case of A-V block is neither practical nor warranted, as this technique requires a sophisticated laboratory setup and is an invasive one. *Fortunately*, the above classification of types A and B fairly accurately localizes the level of conduction failure as above (type A) or below (type B) the bifurcation of the His bundle in most instances. For example, those rare cases of Mobitz Type II block with normal QRS duration have been *shown to result* from a conduction disorder within the His bundle,[77] whereas Wenckebach type of conduction occurring below the A-V junction is usually associated either with a stable wide QRS[91] or progressive widening of the QRS complexes in consecutive beats.[94] *It is true that* type 1 block with widened QRS may result from a combination of intranodal Wenckebach phenomenon and underlying bundle branch block. Hence, assumption of two levels of conduction disturbance *appears* safer in this last variety. Furthermore, this classification can be used in cases of third degree (high grade) A-V block, while types 1 and 2 apply only to second degree block with conduction ratios greater than 2:1.[9, 93]

Finally, the difference between the conventional and the new classifications must be discussed with reference to the basic principles on which they are based. For instance, Wenckebach phenomenon can be observed in sinoatrial block,[58, 60] exit block from an ectopic pacemaker, and even in conduction block between contiguous ventricular *fibers*.[92] Similarly, Mobitz Type II block, or sudden failure of propagation, may also be seen in any region of the cardiac tissue. In other words, the old classification is based on the modes of block or physiologic phenomena. It can further be speculated that type 1 block is perhaps produced by decremental conduction or inhomogeneous *conduction* in tissues having lowered membrane potentials. Possible role of local reentry movement causing *blockage of the final* beat may also be suggested. On the other hand, type 2 block is more likely to result from other mechanisms such as significantly longer action *potential duration* and refractory period of the downstream fibers, or a premature discharge of the distal tissue *leaving a state of* refractoriness. A critical reduction of excitability *in the downstream* fibers, especially with temporal fluctuations *of the safety factor*, is another obvious possibility.[42, 47]

Contrariwise, the new classification of A-V block into types A and B is based on the level of conduction failure, or anatomic considerations, *and cannot be applied to conduction block in* other portions of the cardiac tissue (e.g., S-A block). Thus, if one is primarily concerned with the electrophysiologic mechanisms of A-V block, he should use the old classification, while one might *better use the new classification* if he is interested in the anatomic site of block. In this regard, we must stress the fact that it is essentially the level of conduction failure rather than the local electrophysiologic mechanism that determines the clinical symptoms and prognosis and dictates the mode of treatment.[95] The above discussion provides the strongest argument for the use of the new classification or a combination of the old and new criteria in clinical cardiology, as long as one is aware of its limitations in precisely localizing the site of impaired conduction. *In those selected cases where such* localization is of utmost importance, one always could as well as should resort to His bundle electrography, whereas in a majority of instances, simple and fairly reliable guidelines are obtained by the new criteria discussed above.

Summary

Various electrophysiologic as well as anatomic factors affecting impulse transmission *in general* and A-V conduction in particular have been discussed to illustrate the complexity and diversity of the phenomenon of conduction in the heart. Arguments have also been presented for a new *classification of A-V conduction* block.

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Atrial tachycardia including the so called paroxysmal variety most often is due to reentrant excitation The atrioventricular node usually is the site of the one way block and reentry causing this arrhythmia[6] However the sinus node also can be the site of similar abnormalities of conduction and thus also can be responsible for reentrant tachycardia Unless caused by digitalis atrial tachycardias usually are treated by measures which reflexly increase vagal discharge or by administration of digitalis which probably acts at least in part in the same manner The primary use of quinidine and procaine amide is in preventing recurrences of these arrhythmias Atrial premature depolarizations may require treatment either because they are distressing to the patient or because they initiate more troublesome atrial tachyarrhythmias Either quinidine or procaine amide may successfully abolish or decrease the frequency of atrial premature depolarizations

The treatment of arrhythmias due to the Wolff Parkinson White syndrome often is difficult and many different agents have been employed with varying degrees of success In some cases surgical intervention has been employed Rapid arrhythmias in patients with anomalous atrioventricular pathways usually are initiated by a premature impulse originating in either the atria or ventricles Both quinidine and procaine amide reduce the likelihood of such premature depolarizations Also both the initiation and perpetuation of the tachyarrhythmia requires an appropriate balance between the effective refractory period and conduction velocity in the anomalous atrioventricular pathways and the normal atrioventricular conduction system Both quinidine and procaine amide prolong the effective refractory period of the anomalous pathways and may depress conduction in them to the point of block Thus either agent may terminate a rapid reentrant rhythm or prevent its occurrence At the same time it must be remembered that sufficiently high plasma levels of either drug can prolong refractoriness and slow conduction in the atrioventricular node and His Purkinje system In this manner they may perpetuate or increase the incidence of tachyarrhythmia Finally in patients with anomalous atrioventricular pathways who are in atrial fibrillation quinidine and procaine amide can decrease the ventricular rate by prolonging the effective refractory period of the bypass paths

Patients with the sick sinus syndrome present a wide variety of arrhythmias[10] Their treatment often is associated with considerable risk If atrial fibrillation is abolished it may be found that the sinus and other potential atrial pacemakers are unable to sustain an adequate supraventricular rhythm Treatment of atrial premature depolarizations and atrial tachycardias with depressant drugs such as quinidine and procaine amide may result in marked depression of sinus node activity or the creation of high grade sinoatrial block Atrioventricular junctional arrhythmias respond to treatment with procaine amide with abolition of premature contractions and nonparoxysmal tachycardias in 70 to 80 per cent of cases[1]

Ventricular premature depolarizations can result from a wide variety of causes If they result from recent myocardial infarction lidocaine usually is the treatment of choice because control can be established rapidly and safely Procaine amide also can be used intravenously to control such arrhythmias by combining a series of intravenous injections with a constant rate infusion (see below) Also oral procaine amide probably is used most frequently to maintain control of these arrhythmias when a lidocaine infusion is to be terminated Oral quinidine can be used for the same purpose and can be tried if procaine amide is not effective

If ventricular premature depolarizations result from digitalis intoxication and require immediate treatment either lidocaine or diphenylhydantoin would be the agent of choice It should be remembered however that procaine amide can be used to treat ventricular arrhythmias caused by digitalis although it may prove troublesome For ventricular premature depolarizations not caused by recent infarction or digitalis the need to treat and the choice of agent must be evaluated in relation to the individual patient For all patients with ventricular premature depolarizations suppression can be expected in 80 per cent of those treated with procaine amide[1]

Ventricular tachycardia may respond to either quinidine or procaine amide but now treatment ordinarily would be with lidocaine or countershock However procaine amide or quinidine can be used both to terminate and to prevent the recurrence of ventricular tachycardia or fibrillation in the majority of patients

Electrophysiology and pharmacology of cardiac arrhythmias VII Cardiac effects of quinidine and procaine amide A

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Quinidine and procaine amide are the oldest of the commonly used antiarrhythmic drugs, and remain amongst the most effective for control of atrial and ventricular arrhythmias Quinidine, a cinchona derivative and the d isomer of quinine, was initially used for the therapy of malaria, following its preparation by Pasteur in 1853[1] That cinchona derivatives could be used successfully in the therapy of cardiac rhythm disorders was known as early as 1749 , however it was not until Frey s 1918 report of the effects of cinchonine, quinine and quinidine in patients with atrial fibrillation[3] that the efficacy of the latter drug was fully recognized and its use extended to the treatment of other cardiac arrhythmias

The use of procaine amide is the direct result of studies by Mautz in 1936 which showed that procaine increased the threshold to electrical stimulation of ventricular myocardium[4] Because procaine has a short duration of action due to rapid hydrolysis by plasma esterases and because it has prominent toxic effects on the central nervous system, its congeners were studied in an effort to find a longer acting drug with comparable antiarrhythmic action and less central nervous system toxicity The result of these studies was the application of procaine amide to clinical cardiac therapy

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Treatment of specific arrhythmias

Quinidine and procaine amide are useful for prophylaxis and treatment of a wide range of atrial and ventricular arrhythmias Either drug can be used to convert atrial fibrillation or flutter to a regular sinus rhythm although in many instances electrical countershock is employed If either drug is administered as the primary therapeutic agent there is a risk that the ventricular rate may increase to undesirably high levels This results primarily from a drug induced decrease in atrial rate which reduces the repetitive concealed conduction of atrial impulses in the atrioventricular junction As a consequence, a greater fraction of the impulses entering the A V junction may propagate to the ventricles The increase in ventricular rate also may be due in part to a vagolytic effect of quinidine and procaine amide which has been clearly demonstrated in experimental animals but may not be important in man[5] Because of the risk of an excessive increase in ventricular rate digitalis should be administered in doses sufficient to increase the effective refractory period of the atrioventricular junction before attempting to treat either atrial flutter or fibrillation with quinidine or procaine amide

The greatest use of both agents in relation to treatment of atrial flutter or fibrillation is in preventing the recurrence of these arrhythmias If fibrillation has been present for years or has recurred frequently neither drug is likely to prevent its return On the other hand, if the arrhythmia has been of short duration, if the atria are not greatly enlarged and if there has been successful surgical replacement of the mitral valve, administration of either drug may be associated with maintenance of normal sinus rhythm for long periods of time

dose If there is periodic recurrence of arrhythmia or periodic appearance of electrocardiographic evidence of toxicity the dosing interval should be shortened to four hours and the size of the dose reduced appropriately

If a steady plasma level of procaine amide has been established by constant intravenous infusion and a change to oral administration is planned the first dose should not be given until four hours after termination of infusion If this precaution is not observed plasma levels are likely to reach toxic levels after the first oral dose if the level at the termination of infusion is in the upper half of the therapeutic range (Fig 2)

While procaine amide can be administered by intramuscular injection this route usually is employed only for patients who are unable to take oral medication The other frequent route of administration is intravenous Procaine amide can be administered either by intravenous injection constant rate intravenous infusion or both If the intravenous route is employed for rapid control of an arrhythmia repeated intravenous injections are needed because of the relatively long time (>6 hrs) required to establish an effective plasma level by infusion at reasonable rate Usually the total dose used for intravenous injection is not greater than 1 Gm This can not be administered safely as a single injection because of adverse effects on electrical and mechanical activity of the heart and on systemic vascular resistance

A schedule of administration which is safe and effective is the following Procaine amide is administered in doses of 100 mg at intervals of 5 minutes and blood pressure and ECG are monitored after each dose An intravenous infusion at a rate of 20 to 80 μg/kg /min is started simultaneously with the first dose The intravenous injections are terminated either when the desired effect is achieved or a total of 1 0 Gm has been administered With this method an effective plasma concentration in the range of 3 to 10 μg/ml is achieved rapidly and safely The need to administer the drug at intervals of five minutes results not from the half time for elimination but from the rapid equilibration of the procaine amide in an apparent volume of distribution of 1 5 to 2 5 L/kg This rapid equilibration causes plasma levels to fall rapidly ($t^{1/2}$ = 9 min) after each intravenous injection

It has been shown for procaine amide and it probably is true also for quinidine that the apparent volume of distribution of the drug is reduced in patients with congestive heart failure In such patients therefore a given dose may result in a higher blood level than would be attained in the absence of failure

Metabolism and elimination Procaine amide is eliminated both by hepatic metabolism and renal excretion Between 75 to 95 per cent of a given dose is eliminated in the urine 30 to 60 per cent appears as procaine amide and the remainder as metabolites The major metabolite in humans is N acetyl procaine amide (NAPA) [4,13] The rate of conversion of procaine amide to NAPA varies widely among different subjects and this variability may be related to the occurrence of some forms of toxicity particularly the development of a lupus like syndrome At present the biologic activity of NAPA and other metabolites is not completely known Additional information on this and on procaine amide metabolism is essential since in a given individual NAPA may represent more than 50 per cent of the total drug (procaine amide + NAPA) present in the plasma [1] The implications of this are serious If NAPA exerts effects on the heart like those of procaine amide measurement only of the procaine amide level may provide a completely erroneous indication of the total concentration of antiarrhythmic drug Approximately 15 to 25 per cent of procaine amide is bound to plasma protein values for binding of NAPA are not available Elimination of procaine amide in the urine is slowed by impaired renal perfusion of function as in heart failure or shock or by alkalinization of the urine Since procaine amide is a weak base in alkaline urine more drug is present in the uncharged form and thus can diffuse back into the plasma from renal tubular fluid The renal excretion of NAPA appears to be similar to that of procaine amide [1]

Undesirable effects The effects of procaine amide on the cardiovascular system are for the most part dose related and are discussed below In addition procaine amide has many other undesirable side effects Prominent among them are nausea vomiting and diarrhea during oral administration of large daily doses Also encountered are rashes chills and fever agranulocytosis and mental disturbances including rare depression psychosis or convulsions Of real importance during chronic drug administration is the

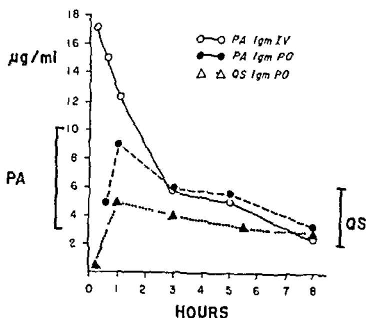


Fig 1 Plasma concentrations of procaine amide (*PA*) and quinidine sulfate (*QS*) Plasma concentration in μg/ml is plotted on the vertical axis time in hours on the horizontal The bracket on the left indicates the *range of therapeutic* plasma procaine amide concentrations, that on the right therapeutic quinidine concentrations The curves plotted are for PA 1 Gm administered orally and 1 Gm administered intravenously and for QS 1 Gm administered orally (Modified after Mark L C Kayden H J Steele M et al The physiological disposition and cardiac effects of procaine amide *J Pharmacol Exp Ther* 102 5 1951 and Bellet S ref 22)

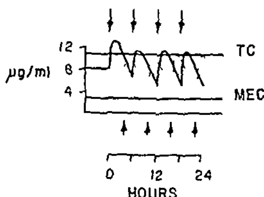


Fig 2 Effect of changing from intravenous to oral administration of procaine amide Plasma procaine amide concentration (μg/ml) on vertical axis time (hours) on horizontal *Line TC* = toxic concentration *MEC* = minimum effective concentration Patient has plasma concentration of 8 μg/ml as result of *continuous intravenous infusion Solid arrows and* curve indicate the time of administration of procaine amide 1 Gm po/q 6h and the resultant plasma concentrations In this instance oral procaine amide therapy is initiated immediately on discontinuing the intravenous infusion and the oral doses result in transient attainment of toxic plasma concentrations Dotted arrows and curve indicate same mode of oral therapy *the only exception* being that four hours passed between cessation of intravenous therapy and initiation of the oral *regimen In this instance plasma levels remained entirely* within the therapeutic range (Modified after Bigger J T Jr and Giardina E G V ref 11)

Arrhythmia prophylaxis post infarction

Studies conducted to evaluate the prophylactic value of procaine amide and lidocaine in patients admitted to intensive care units for recent myocardial *infarction* have *not clearly* demonstrated that either agent has an appreciable effect on mortality Nevertheless if there is a reasonable likelihood that premonitory arrhythmias may not be identified promptly in such patients and if there is no clear contraindication to prophylactic antiarrhythmic therapy, use of procaine amide should be considered for patients with coronary artery disease and chronic or recurrent ventricular arrhythmias Satisfactory data is not available *concerning the effectiveness (in terms of* mortality) of prophylactic administration of antiarrhythmic agents However, there is evi*dence that both quinidine and procaine amide* as chronic oral medication may decrease the incidence of ventricular premature depolarizations in this patient population[11]

Clinical pharmacology

A Procaine amide

Administration Procaine amide is administered by mouth in a total daily dose of 1 to 6 grams to initiate treatment of arrhythmias which do not require immediate termination or to continue treatment on a long term basis after intravenous medication with procaine amide or *other antiarrhythmic therapy* After an oral dose the peak plasma level and cardiac effect usually are attained within 1 to 2 hours (Fig 1) and with *repeated oral doses the plasma level* attains its steady state plateau value after 24 to 48 hours Procaine amide is almost completely absorbed *from the small intestine where the pH is* alkaline delayed gastric emptying thus will slow absorption and both delay the peak plasma level and *decrease its magnitude The usual range of* therapeutic plasma levels is between 3 to 10 μg/ml[13] There is some indication that within this range *higher levels are needed to treat* patients with atrial fibrillation or flutter than patients with other arrhythmias The average t½ for elimination of procaine *amide is 3 to 4 hours* in normal adults for this reason the plasma level falls fairly rapidly after each dose Consequently if oral doses are given *at intervals of 6 hours* the plasma level may vary from a value less than the minimum effective concentration just before the dose to a *toxic concentration one hour after the*

Annotations

Acute renal failure associated with cephalosporin therapy

We wish to emphasize the risk of nephrotoxicity if prolonged and/or high doses of cephalosporins are used Cephaloridin and cephalothin were responsible for acute renal failure (ARF) in eight patients with previous normal renal function observed between 1967 and 1973 four of them had bacterial endocarditis.

ARF after cephaloridin

Case 1 A 47 year old man had aortic incompetence with bacterial endocarditis. Blood cultures showed *Staphylococcus albus* Prolonged anuria occurred 10 days after the start of treatment with cephaloridin (6 Gm per day) Hemodialysis was required twice but the patient died from cardiac failure Renal histologic examination showed acute tubular necrosis glomeruli and vessels were normal

Case 2 A 66 year-old man had bacterial endocarditis due to *Streptococcus hemolyticus* Combined treatment with cephaloridin (4 Gm per day) and streptomycin (1 Gm per day) was given during 41 days Anuria then occurred requiring peritoneal dialysis twice Diuresis resumed but the patient died from cerebral hemorrhage Renal histology showed diffuse tubular atrophy with focal interstitial fibrosis and edema and infiltration by lymphomonuclear cells

Case 3 A 65-year old man had aortic stenosis with evidence of bacterial endocarditis Anuria occurred after he received cephaloridin (6 Gm per day) for 10 days Peritoneal dialysis was started but the patient died from persisting hypotension High serum levels of cephaloridin (9 µg per milliliter) were found 24 hours after the beginning of peritoneal dialysis Diffuse interstitial edema with focal cellular infiltration was found on renal histologic examination

Case 4 A 76-year-old man with bacterial spondylitis was treated with cephaloridin (6 Gm per day) in combination with gentamicin (1[illegible]0 mg per day) for three weeks Oliguria with a rise in blood urea level occurred Diuresis resumed spontaneously eight days later and the patient fully recovered

Since 1965 more than twenty cases of ARF after administration of cephaloridin have been reported according to a recent review by one of us Anuria was observed in most of these patients and lasted for seven to 13 days requiring one or more hemodialysis treatments. Daily doses of cephaloridin given were usually equal to or above 4 Gm often between 6 and 1[illegible] Gm Total doses of cephaloridin ranged between [illegible]8 Gm over seven days and 304 Gm over 38 days Previous renal function was usually normal in these patients When performed renal histologic examination showed acute tubular necro is with interstitial edema and lymphomonuclear infiltration

Two facilitating circumstances may be responsible for renal damage in patients with bacterial endocarditis treated with cephaloridin (1) prolonged treatment with high doses of this drug and (2) a disturbance in renal hemodynamics due to cardiac failure leading to high intrarenal tissue concentrations of cephaloridin

ARF after combined treatment with cephalothin and gentamicin

Case 5 A 38-year-old woman had regional enteritis with an acute episode of diarrhea due to *Staphylococcus aureus* Cephalothin (12 Gm per day) and gentamicin (240 mg per day) were prescribed for 27 days after which anuria occurred and the blood urea was 250 mg per 100 ml Diuresis ensued after high doses of furosemide A renal biopsy was performed (thirty seventh day) and showed diffuse tubular atrophy with interstitial edema The patient recovered Four months later creatinine clearance was 9[illegible] ml per minute

Case 6 A 32 year old woman was treated for ulcerative colitis with a combination of cephalothin (10 Gm per day) and gentamicin (240 mg per day) Anuria occurred 12 days later the blood urea was 200 mg per 100 ml Anuria reversed after high doses of furosemide and full recovery was observed A renal biopsy (forty fifth day) showed tubular atrophy with interstitial edema

Case 7 A 63 year old man had bacterial endocarditis due to *Staphylococcus aureus* Combined treatment with cephalothin (12 Gm per day) and gentamicin (320 mg per day) was given Nine days later a high output acute renal failure was diagnosed The blood urea was 1[illegible]0 mg per 100 ml Full recovery was observed

Case 8 A 71 year old man had septicemia due to *Staphylococcus aureus* Apyrexia was obtained after treatment with cephalothin (12 Gm per day) and gentami in (320 mg. per day) Anuria occurred 17 days later requiring five hemodialysis treatments but the patient recovered

Few cases with probable nephrotoxicity due to cephalothin have been reported High doses of cephalothin were given to these patients 8 to 24 Gm daily for eight to 35 days Reversible anuria was often present When performed renal histology revealed acute tubular necrosis with or without interstitial involvement

It is likely that in patients treated with cephalosporins the risk of nephrotoxicity may be enhanced by the simultaneous administration of gentamicin Doses of cephalosporin exceeding 4 Gm per day and doses of cephalothin exceeding 6 Gm per day (i.e 100 mg per kilogram per day) should be avoided especially if usual doses of gentamicin (i e 240 mg per day or 4 mg per kilogram per day) is to be prescribed Particular caution is needed in patients at high risk i.e in older and/or dehydrated patients with previous cardiac failure or arrhythmias Such features are frequently encountered in patients with bacterial endocarditis and lead to a subsequent increase in renal interstitial concentration of antibiotics If prolonged

occurrence of a syndrome resembling systemic lupus erythematosis[16] This will occur in perhaps 40 per cent of all patients on chronic oral procaine amide Common symptoms and signs include arthralgia, fever and hepatomegaly, and pleuro pneumonic pathology Symptomatic patients show positive tests for antinuclear factor and lupus erythematosus cells Usually symptoms disappear soon after termination of therapy but positive tests for antinuclear factor and lupus ery thematosus cells revert more slowly The prob able relationship of this reaction to abnormalities of acetylation recently has been described[15]

B Quinidine

Administration Ordinarily quinidine is admin istered orally as quinidine sulfate in divided doses at intervals of 4 to 8 hours to provide a total daily intake of 1 2 to 2 4 grams It can be given intra muscularly or intravenously but the latter route is almost never used because of the associated undesirable effects on the heart and circulation (see below) When quinidine is administered by mouth absorption is almost complete After a single oral dose the plasma level attains a peak value within 1 0 and 2 0 hours (Fig 1) and with repeated oral doses the plasma level attains the plateau value after two to three days When given intramuscularly the peak plasma level occurs at the same time as after oral administration but the value is only 70 per cent of that attained after a comparable oral dose The usual range of thera peutic plasma levels is between 2 and 6 μg/ml lower levels seldom are effective and higher ones frequently are associated with toxicity In most instances the range of plasma levels needed for treatment of atrial arrhythmias, such as fibrilla tion and flutter, are higher than those required for suppression of ventricular arrhythmias The t½ for elimination of quinidine is six to seven hours plasma levels thus fluctuate less markedly during repeated oral dosing than is the case for procaine amide Quinidine also is available as long acting preparations such as quinidine polygalac turonate and long acting quinidine gluconate These preparations need be administered at less frequent intervals than quinidine sulfate and are reported to cause fewer gastrointestinal side effects When these preparations are used the dose should be calculated in terms of the amount of quinidine base contained in each tablet

Metabolism and elimination Approximately 80 per cent of absorbed quinidine is bound to plasma albumin, the extent of binding is depen dent on pH Quinidine also enters red cells where it is bound to hemoglobin, and rapidly equili brates with most body tissues Circulating quin idine is metabolized in the liver and only about 20 to 50 per cent is excreted unchanged in the urine Hydroxylation is the primary metabolic step and several metabolites are formed Little is known about the biologic activity of the metabolites but most are probably less active than the parent drug and most are excreted in the urine Because quinidine depends both on hepatic metabolism and renal excretion for elimination, blood levels will depend on adequacy of both hepatic and renal perfusion as well as on renal function Like procaine amide quinidine is a weak base and its renal elimination will be decreased by alkaliniza tion of the urine

Undesirable effects The effects of quinidine on the cardiovascular system are discussed in a subsequent section In addition to cardiovascular toxicity, quinidine can exert many other undesir able effects Like other cinchona alkaloids quin idine can cause cinchonism and, when severe this may be associated with marked tinnitus loss of hearing blurring of vision, diplopia photophobia and altered color perception With more severe intoxication there may be severe headache confu sion, delirium or psychosis Nausea and vomiting may be present and accompanied by abdominal pain Most frequently quinidine administered orally causes only gastrointestinal disturbances including nausea loss of appetite, vomiting and diarrhea, these symptoms are the most frequent reasons for patients to discontinue taking the drug Quinidine can cause thrombocytopenia by interacting with platelets and platelet antibody and causing lysis of the platelets After cessation of drug administration platelet counts usually return to normal within seven to ten days Rarely quinidine causes anaphylactic reactions and some patients may demonstrate hypersensitivity to the drug and develop fever which disappears when treatment is stopped In patients taking oral anticoagulant drugs quinidine may interact with them and cause unexpected bleeding

Table I Identical effects of magnesium sulphate and of CCK PZ on the gastrointestinal tract*

Action	*MgSO*	*CCK PZ*
Gallbladder contraction	23 25-28†	Primary action
Relaxation of sphincter of Oddi	30	3? 33
Small intestinal motor activity	13	34-37
Colonic motor activity	14 15	38-40
Small intestinal secretion	16	50-54
Decreased sodium and water absorption by small intestinal mucosa	18	49 51 53
Gastric secretion	20 21	46 47
Pancreatic secretion	20	Primary action
Purgation	Primary action	41-43

*Effects of oral or intraduodenal magnesium sulphate in all cases except for the small intestinal secretion studies when MgSO solutions were placed into isolated loops of small intestine
†Numbers indicate the references documenting each action

later following a suggestion by Meltzer Lyon reported that intubation directly into the duodenum of magnesium sulphate in solutions of various strengths and various amounts is followed shortly afterwards (within from 2 to 15 minutes in most cases) by the evacuation of bile into the duodenum and other workers soon confirmed these findings.

Boyden and Birch carried out extensive studies to determine which inorganic ions were the most effective in causing gallbladder evacuation concluding that the Mg and SO ions (i.e. those with the strongest purgative action) were the most effective Further studies of gallbladder contraction and of relaxation of the sphincter of Oddi suggested that magnesium sulphate exerts its effect not by a local action but by causing release of a gallbladder contracting hormone (CCK)

Besides its action on the gallbladder and sphincter of Oddi, CCK has potent motor effects on the intestinal tract A striking increase in small intestinal motor activity follows within 1 to 2 minutes of an intravenous injection of CCK Transit time is decreased and like magnesium sulphate CCK has been used to speed up the passage of contrast media through the small intestine Increased motor activity in the large intestine after intravenous CCK has been demonstrated both in normal subjects and in patients with the irritable bowel syndrome Purgation occurs quite commonly after intravenous injections or infusions of CCK and this same effect produced by the structurally very similar CCK analogue cerulein has been successfully used in the treatment of paralytic ileus

The actions of upper small intestinal extracts on gall bladder contraction (cholecystokinin) and on pancreatic secretion (pancreozymin) are now believed to be due to a single peptide and the names have been combined to cholecystokinin pancreozymin (CCK PZ) Just as CCK PZ has motor effects on parts of the gastrointestinal tract other than the gallbladder so it has secretory actions on intestinal glands other than the pancreas Gastric secretion is weakly stimulated but probably more important is the stimulation of small intestinal secretion[**] This action of CCK PZ could account for the active secretion of fluid into the intestine which occurs in response to the saline purgatives

The data cited above indicate that saline purgatives such as magnesium sulphate have a complex series of actions, both secretory and motor on the gastrointestinal tract these actions being responsible for the purgative effect All the known actions of oral magnesium sulphate on the gut can be reproduced by CCK PZ (see Table I) a hormone which is released by the small intestinal mucosa in response to magnesium sulphate and other saline purgatives We suggest therefore that the mechanism of action of magnesium sulphate and other saline purgatives is as follows

First the CCK PZ released as the salts enter the duodenum stimulates small intestinal and pancreatic secretion and at the same time decreases reabsorption of sodium chloride and water with a resulting increase in the volume of intestinal contents

Secondly as a result of the motor effects of CCK PZ this large volume of fluid (containing the salts) is carried rapidly through the small intestine to reach the colon the rapid transit also tending to impair reabsorption The colon is thus presented with an unusually large volume of fluid to reabsorb

We are not aware of any studies of the effects either of CCK PZ or of poorly absorbed ions such as Mg or SO on colonic absorptive function but it is possible that either or both could interfere with the normal colonic absorption of water and electrolytes Other factors might act in a similar way (bile salts for example excessive amounts of which might enter the colon as a result of rapid transit through the ileum) The net effect of these various factors could be to impair the ability of the colon to reabsorb the large amount of fluid suddenly presented to it

Finally the CCK PZ released by the salts has a direct motor action on the colon itself

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This paper is based on an hypothesis first published in *The Lancet*[56]

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treatment is required serum levels of antibiotics should thus be monitored and the patient's renal function carefully followed

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Mode of action of the saline purgatives

Inorganic salts such as magnesium sulphate have been used as purgatives for hundreds of years It is likely that on a weight basis the quantities of the saline purgatives which have been prescribed since their introduction are greater than for any other medicament listed in current pharmacopoeias Despite the appearance of other preparations which have tended gradually to displace them they still account for a considerable proportion of the estimated 12 million dollars spent on over the counter laxatives in England and Wales each year[1 2] and they retain a similar degree of popularity in the United States They are generally assumed to act solely as osmotic purgatives —the ions being poorly absorbed and sucking water into the gut lumen by osmosis thereby producing a more bulky and more liquid stool However a large body of experimental work has demonstrated that these salts have a complex series of actions both motor and secretory on the gastrointestinal tract which cannot be explained by a simple osmotic effect All the known actions of magnesium sulphate on the gut are closely similar to reported actions of the hormone cholecystokininpancreozymin (CCK PZ) which is released from the intestinal mucosa in response to magnesium sulphate and other salts This paper suggests that the action of the saline purgatives is not brought about by osmotic effects but is in large part due to release of the hormone cholecystokinin pancreozymin (CCK PZ) which has powerful motor and secretory effects on the gastrointestinal tract

Spa waters containing inorganic salts have for centuries been taken for their purgative action Such treatment at the Carlsbad spa for example is said to date at least from the reign of Charles IV (1316 78) while in the United Kingdom the refusal of Henry Wicks oxen to drink the bitter tasting water from a spring at Epsom is said to have led to the use of this water and its salts from the year 1618[4] Waters with cathartic properties usually contain magnesium sulphate (e g Epsom salts) or sodium sulphate (e g Carlsbad salt or Marienbad salt) the active constituents being the Mg and SO ions (some other ions such as phosphate or tartrates have a similar but weaker effect) These salts act usually within 1 to 2 hours of being taken by mouth on an empty stomach Modern textbooks of pharmacology and therapeutics are convincingly uniform in their explanations of their mode of action they are slowly and incompletely absorbed from the digestive tract and retain water in the intestinal lumen by osmotic forces and as a result the intestinal contents are increased in bulk " There is however considerable evidence that the saline purgatives have a far more complex mode of action than is generally believed

The saline purgatives produce a striking increase in intestinal motor activity especially in the small intestine This effect has been used for increasing the rate of transit of contrast media during radiological studies of the gut and for aiding the expulsion of small intestinal worms[1] It seems unlikely that this hyperperistalsis can be attributed to "stretching of the wall of the intestine or to increased intraluminal pressure resulting from retention within the gut lumen of abnormally large quantities of fluid because a similar effect can be produced by quite small quantities of saline purgatives in isotonic solution Magnesium sulphate also stimulates motor activity in the large intestine

The increase in the volume of intestinal contents produced by saline purgatives was attributed to a simple osmotic effect over a century ago An extensive series of experiments led Hay to suggest that the fluid was produced by intestinal secretion rather than transudation Loewy ' found an increase in oxygen consumption and carbon dioxide output after various doses of sodium sulphate and Lium and Florey attributed this to stimulation of oxygen dependent intestinal secretion by the salt These workers demonstrated that isotonic magnesium sulphate affected transport of water and sodium across the small intestinal wall of cats decreasing net absorption It seems probable therefore that the saline purgatives stimulate a net intestinal secretion and that this is an active process and not due to passive osmosis Furthermore this is an effect not due directly to the action of the ions themselves on the intestine but brought about by some other mechanism presumably either reflex or humoral Intraduodenal magnesium sulphate also stimulates the secretion of enzyme rich pancreatic juice[9] and is a weaker stimulant of gastric secretion[r n] The increased volume of intestinal contents produced by MgSO and other saline purgatives is thus contributed to in varying degrees by a flow of gastric pancreatic and intestinal juices

On the first recorded occasion that a duodenal tube was used on a patient Hemmeter in 1895 provoked a flow of bile by injecting Carlsbad water into the duodenum[n] Some years

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Of recording your own blood pressure

Apparatus designed for self recording of blood pressure is readily available Patients are advised and trained by some physicians to record their own blood pressures This is done in spite of the fact that squeezing the sphygmomanometric bulb to inflate the cuff wrapped around one s own arm results in a variable elevation in one s arterial blood pressure The change produced in arterial blood pressure varies among patients and even from moment to moment in the same patient The reason for recording the patient s blood pressure at home is to learn the level of his arterial blood pressure without the introduction of an artificial undesirable and unpredictable variable In order to demonstrate the effect of recording one s own blood pressure on the blood pressure level a study was done in which the arterial blood pressures of 20 subjects selected at

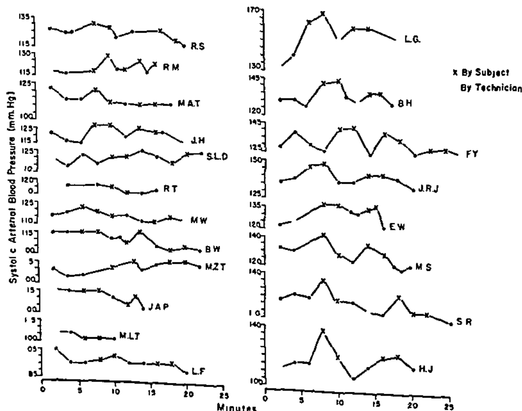


Fig 1 Influence of *self recording* of blood pressure on systolic blood pressure in 20 subjects

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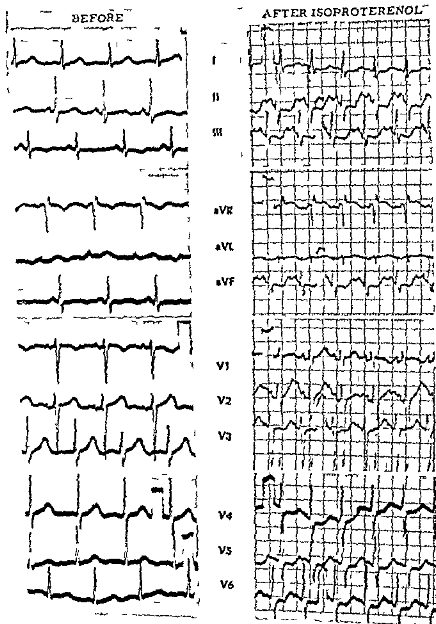


Fig 1

the dangers of overdose adverse reaction and consequent cardiomyopathy are often minimized

In this regard we have reviewed our patient records to identify in tances of isoproterenol adverse reactions *Retro*spectively we have found eight cases of documented isoproterenol toxicity at therapeutic dosages Among these cases, two patients developed acute myocardial *infarction* with concomitant tachycardia substernal chest pain hypotension and serum enzyme changes consistent with myocardial infarction Electrocardiographic findings *of large depressed S T* segment shifts were seen in the precordial l ads. One of these *patients* died following this isoproterenol induced ischemic episode *The electrocard ogram* of the other patient (a 4? year-old female) is shown in Fig 1 After *isoproterenol* inhalation (on the right) *there are large* negative S T segment shifts This patient had no prior history of coronary *heart disease* and was completely asymptomatic until this point

The third patient (a 3 year old female) receiving an isoproterenol drip following cardiac surgery developed reversible subendocardial ischemia with large *negative* S T segment shifts reverting to normal after cessation of the intravenous infusion. This is clearly noted in Fig 2 the upper tracing being before isoproterenol and *the lower tracing* being immediately after The remaining five cases consisted *of* patients with bronchial asthma who demonstrated periods of transient myocardial *ischemia* as evidenced by abnormal negative S T segment shifts in their *electrocardiograms* Characteristic chest pain in these patients was reli ved by *termination* of

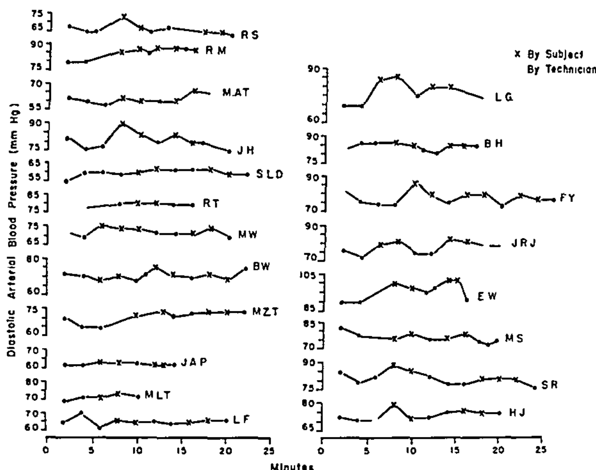


Fig 2 Influence of self recording of blood pressure on diastolic blood pressure in 20 subjects

random were recorded first by a technician and then alternately by the subjects themselves a few minutes later Figs 1 and 2 summarize the results In most instances a higher level of blood pressure was obtained when the subjects recorded their own pressures some being markedly increased Therefore to obtain better and more desirable information the patient s blood pressure should be recorded by a well trained calm person and not by the patient himself

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Isoproterenol toxicity

The sympathomimetic amine isoproterenol is used clinically as a bronchodilator in respiratory disorders and as a cardiac stimulant in cardiogenic shock after myocardial infarction circulatory failure heart block and septicemic shock As a direct beta stimulant it acts as a smooth muscle vasodilator and as a chronotropic and inotropic agent

However by potentially increasing myocardial oxygen consumption these actions may be harmful in patients with coronary artery disease or severe mitral or aortic stenosis Sudden death has been reported after the use of isoproterenol[3,7] and arrhythmias have been precipitated by this agent[4] Palpitation tachycardia headache flushing and anginal pain have also been reported following its use[2] Exaggeration of arterial hypoxemia[13] and the locked lung syndrome [5] have also been found in patients being treated for bronchial asthma

Microscopic and gross alterations in structure and ultrastructure have been demonstrated in experimental animals following wide dose ranges of isoproterenol[4] The severity of the lesions was found to be dependent upon dose and route of administration These toxic manifestations have been described as infarct like myocardial necrotic lesions Their presentation closely resembles that of subendocardial infarction and ischemia in man There is definite evidence that isoproterenol can be a source of cardiomyopathy in man and should be classified as a preventable or reversible form of cardiac disease

Although isoproterenol is an effective pharmacologic agent

16 Rona G Chappel, C I Balazs T and Goudry R An infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat Arch Pathol 67 443 1959
17 Horn, H Field L E Dack S and Master A M Acute coronary insufficiency pathological and physiological aspects AM. HEART J 55 63 1950
18 Levine H D and Ford R B Subendocardial infarction report of six cases and critical survey of the literature Circulation 1 246 1950
19 Morin Y and Cote G Toxic agents and cardiomyopathy In Cardiomyopathy Burch G E editor Cardiovascular Clinics 4 245 1972
20 Winsor T Mills B Howe B B Winbury M and Berger H J Intramyocardial diversion of coronary blood flow effects of isoproterenol induced subendocardial ischemia Microvasc Res In press
21 Baker L D Snow J A Pompsiello J C Sharma G and Messer J V Isoproterenol induced coronary steal metabolic observations in human coronary artery disease Clin Res 17 228 1969 (Abstr)
22 Downey H F Bashour F A Mandel T Kechejian S J and Underwood R H Effect of isoproterenol on collateral blood flow in ischemic myocardium Clin Res 21 817 1973 (Abstr)
23 Klein H O and Berger H J Synergistic actions of nitrite beta adrenergic blocking agents in the therapy of angina pectoris the pharmacologic and therapeutic rationale Cardiology In press 1973

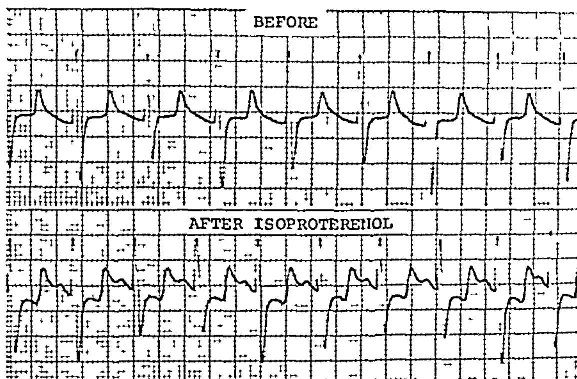


Fig 2 *Top panel* before isoproterenol *Lower panel* after isoproterenol administration

isoproterenol therapy administration of sublingual nitroglycerin or by inhalation of oxygen

When signs of isoproterenol toxicity become evident the drug should be discontinued immediately We have found that the electrocardiogram is a reliable and sensitive method to delineate the deleterious effects of isoproterenol We suggest that the S T segment of the electrocardiogram be monitored for acute negative depressions which may be the first sign of isoproterenol induced subendocardial ischemia

We have recently reported that isoproterenol selectively produces an intracardiac diversion of blood flow away from the subendocardium toward the epicardium in the ischemic dog heart Recent investigations have also noted that isoproterenol decreases collateral flow to ischemic areas by dilation of normal vessels[2] These phenomena have been described as a coronary steal

Our experimental studies show that combined use of a beta blocker and a nitrate completely reverses the abnormal electrocardiographic findings caused by isoproterenol Neither the beta blocker nor the nitrate alone were able to totally reverse the ischemic S T segment shift caused by isoproterenol These results are in agreement with numerous clinical studies demonstrating the beneficial synergistic actions of these drugs[13] We have also demonstrated our experimental finding in preliminary clinical trials

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3 Exon P D Pressurized aerosols in asthma Br Med J **1** 177 1967
4 Greenberg M J and Pines A Pressurized aerosols in asthma Br Med J **1** 563 1967
5 Kerr J W Deaths from asthma Br Med J **1** 177 1967
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8 Graham O S and Shields W O Cardiac arrest in bronchial asthma Med J Aust **1** 524 1955
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10 Millar M and Semple T Cardiac arrest in asthma Br Med J **2** 498 1964
11 Lockett M F Dangerous effects of isoprenaline in myocardial failure Lancet **2** 104 1965
12 Speizer F E Doll R Half P and Strang L B Investigation into use of drugs preceding death from asthma Br Med J **1** 339 1968
13 Fordham R F and Resnekov L Arterial hypoxemia A side effect of intravenous isoprenaline used after cardiac surgery Thorax **23** 19 1968
14 Greenberg M J Isoprenaline in myocardial failure Lancet **2** 442 1965
15 Van Metre T E Adverse effects of inhalation of excessive amounts of nebulized isoproterenol *in status* asthmaticus, J Allergy **43** 101 1969

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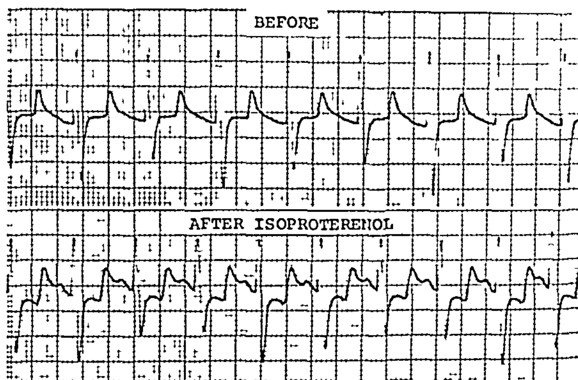


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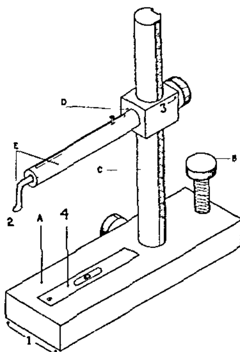


Fig 1 Diagrammatic representation of a commercially available device to aid in measuring jugular venous pressure

simple but accurate device for measuring the JVP has therefore been constructed I would like to share the idea of this device with your readers

The device (Fig 1) consists of a base (*A*) with an inbuilt spirit level (*4*) and a level adjustment screw (*B*) Into the base fits a vertical rod (*C*) bearing a 15 cm long scale A horizontal rod (*D*) with the reading edge (*3*) can be slid up and down along the vertical rod The former encloses as its core another rod (*E*) which can be slid backward and forward The S shaped outer end of the rod (*E*) is so constructed that when (*D*) is slid down to the lowest level the pointer (*2*) comes exactly in line with the lower surface of the base the edge (*3*) then reads zero on the scale As the rod (*D*) is slid above the edge (*3*) reads the vertical distance between (*1*) and (*2*) The various parts of the device are detachable (and quickly assembled) and can be placed in a box (20 by 5 by 5 cm)

The patient lies on a couch with his head slightly turned toward one side and the trunk elevated to a given angle (commonly about 45 degrees) The device is placed over the patient s chest with the edge (*1*) of the base resting against SA The base is made exactly horizontal with the help of the level adjustment screw (*B*) and the spirit level (*4*) The horizontal rods (*D*) and (*E*) are so adjusted that the pointer (*2*) comes at the level of UJV The JVP is now read on the scale with the help of the reading edge (*3*)

The device is commercially available from M/s Sur Nib Company 121/631 Shastri Nagar Kanpur (U P) India

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REFERENCE

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Letters to the Editor

Aortic valve disease surgery

To the Editor

The Editorial Surgery for aortic valve disease in the December 1974 issue of the JOURNAL (AM HEART J 88 683 1974) was generally a thoughtful and conservatively stated position which indicated that aortic valve replacement should not be done in the symptom free patient but that there appeared to be a justifiable trend in that direction The line of reasoning was that truly successful surgery would have to occur prior to the development of irreversible myocardial damage

Against operation in asymptomatic patients with aortic stenosis is the limitation of what can be done surgically short of valve replacement and the short expectancy of prosthetic valves at present to say nothing of the dangers of embolization and the requirement for anticoagulation The number of youngsters who have congenital aortic valve anomalies is very large and the great majority of these are asymptomatic and do not require surgery by standards of even the most wildly enthusiastic surgical proponents For a youngster of 15 a long term follow up involves a great deal more than 10 years with any luck at all These patients do quite well in general and probably form the group of patients out of which come the calcific aortic valves in the 40 to 60-year old subjects Given the many years of follow up and the rather stable presence of mild or moderate aortic stenosis more objective grounds for surgical intervention must be present than fear of irreversible myocardial disease I would whole heartedly concur with Drs Galyean Suzuki and Blake in accepting symptoms particularly angina as evidence for surgical intervention but hemodynamic measurements are also necessary to avoid misinterpretation of subjective complaints It was our feeling in 1965 that a valve area of 0 6 cm² per square meter was a value below which surgery was indicated We felt that peak pressures were not a reliable basis and a mean ejection gradient of at least 45 mm Hg is necessary to prove the necessity for surgical intervention

This relatively large reservoir of youngsters with mild to moderate aortic stenosis argues for a conservative approach and that surgical intervention should remain a carefully considered decision with objective criteria no matter how low the mortality rate becomes for putting in an artificial valve Perhaps developments in non invasive techniques such as the echocardiogram will permit recognition of the more marked degrees of left ventricular hypertrophy hopefully before real dysfunction occurs It is unreasonable both to operate early or to perform left heart catheterizations every year for 30 or 40 years In the meantime most of us believe that angina or left ventricular T wave changes still stand as the reasonable indications for left heart catheterization and possible surgery if catheter data substantiate the severity

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1 Morgan B C Guntheroth W G Baum D and Merendino K A Reassessment of operative indication for moderate congenital aortic stenosis J Thorac Cardiovasc Surg 49 150 1965

Reply

To the Editor

We appreciate Dr Guntheroth s interest in our editorial and find no fundamental conflict between our observations and his It seems to us that he a pediatrician is emphasizing the difficulty in knowing when to recommend cardiac catheterization in asymptomatic subjects and is pointing out that findings in the electrocardiogram may help While it is not clear just what he means by left ventricular T wave changes we feel sure that he implies negativity of T in left precordial leads where the QRS is almost completely positive and we know that he is aware of the limitations of the method that the electrocardiogram may be normal in some patients with severe aortic stenosis

We concur with Dr Guntheroth that a conservative approach to children with mild or moderate aortic stenosis is appropriate and share his hope that non invasive techniques may eventually permit an accurate assessment of not only the presence of left ventricular overload by whatever name but also the adequacy of compensatory mechanisms and enable us to recognize their deterioration in time to be able to intervene appropriately

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Jugular venous pressure gauge A bedside device to measure jugular venous pressure

To the Editor

Bedside measurement of jugular venous pressure (JVP) is an important step in the assessment of patients with congestive heart failure as well as of those with hypervolemia/overhydration The principle involved in the measurement of JVP was elucidated by Lewis who emphasised that JVP is the vertical distance between the uppermost limit of the distended/pulsating external/internal jugular vein (UJV) and the sternal angle of Louis (SA) Thus JVP can be measured by placing a centimeter ruler vertically at SA and directing a straight edge held at right angles to the ruler towards the neck at UJV However the results could be fallacious if the ruler is not held exactly vertical and/or if the straight edge is not exactly horizontal moreover if the JVP is normal or only slightly raised the clavicle often comes in the way of the straight edge making the measurement somewhat difficult A

Books received

Exercise Testing in Children Applications to Health and Disease By Simon Godfrey Philadelphia 1974 W B Saunders Company 168 pp

Clinical Perinatology Edited by S Aladjem and A K Brown St Louis 1974 The C V Mosby Company 492 pp

A Programmed Introduction to the Electrical Axis and Action Potential By J Castellanos Jr and Louis Lemberg M D Oldsmar Fla 1974 Tampa Tracings 15? pp

The Year Book of Cardiovascular Medicine and Surgery 1974 By W P Harvey W M Kirkendall J W Kirklin A S Nadas P Oglesby E H Sonnenblick and E S Wright Chicago 1974 Year Book Medical Publishers Inc 479 pp

The Year Book of Endocrinology 1974 By T B Schwartz W G Ryan and F O Becker Chicago 1974 Year Book Medical Publishers Inc 454 pp

Trace Elements in Relation to Cardiovascular Diseases World Health Organization Geneva Switzerland 1974 World Health Organization 45 pp

Studies in Preventive Cardiology Coronary Heart Disease Epidemiology and Rehabilitation By Daniel Brunner Tel Aviv Israel, 1974 Nateev Ltd 232 pp

Principles and Techniques of Human Research and Therapeutics Vol IV Importance of Experimental Design and Biostatistics By F Gilbert McMahon Mount Kisco N Y 1974 Futura Publishing Company 77 pp Price $8 50

Book reviews

Digitalis By Thomas Woodward Smith M D and Edgar Haber M D Boston 1974 Little Brown & Company 110 pages

This small succinct publication on digitalis is from the *Medical Progress Series of the New England Journal of Medicine* It clearly summarizes the present concepts in digitalis administration and further reflects present trends in medicine For example on page 49 the authors indicate that digitalis intoxication has been reduced decidedly with the use *of computers This may impress some clinicians* but to this reviewer it is indeed strange that the brains of present day physicians are unable to program the use of digitalis as well as an inanimate computer especially a clinical problem as simple as the proper digitalization of a patient Furthermore even *with electronic computers* digitalis intoxication is as high as 12 per cent in one series or even 4 per cent in another The incidence of intoxication should be zero if properly used and intoxication could only then occur if the patient fails to follow proper instructions Digitalis intoxication has become one of *the major clinical problems* today and this book fails to teach readers how to avoid it The first sentence on page 41 under Digitoxin is not clear The authors review the pharmacodynamic action of digitalis pharmacokinetics bioavailability clinical use hemodynamic effects and other aspects of the drug They could have included more data on man with critical evaluation of them For example in the discussion on serum and plasma concentration (Chapter 20) the authors fail to indicate clearly how a physician is to decide the next dose of a rapidly excreted drug such as digoxin when the blood sample is collected in the early morning and the physician reviews and sees the patient in the late afternoon and when the physician of course desires to maintain a fairly constant therapeutic level of the drug in his patient for 24 hours This book is interesting and a thoughtful study of the book by an experienced *cardiologist will reveal the nature of the pharma*cologic and clinical problems which exist today with the use of digitalis and why intoxication with the drug is a major cardiologic disease state today

Progress in Cardiology Edited by Paul N Yu M D and John F Goodwin M D Philadelphia 1974 Lea & Febiger 349 pages

Volume 3 of Progress in Cardiology edited by Yu and Goodwin reviews the progress made in recent years in epidemiology and prevention of coronary heart disease selected aspects of electrophysiology and arrhythmia exercise cardiology *role of the renin angiotensin system in the etiology of* hypertension drugs affecting the heart valve placement prevention of thrombosis echocardiography and others Physicians who have been unable to follow the literature closely will find this publication to be especially useful The *respective authors* have condensed very well the important publications related to their respective subjects The field of cardiology is advancing and changing rapidly Therefore this publication is welcomed All physicians who treat heart disease will find this book useful

Blood Flow in Arteries By Donald A McDonald M A D M D Sc. Baltimore 1974 The Williams & Wilkins Company 496 pages

This book on the fundamental physical principles governing blood flow through the arterial system should interest physiologists and others engaged in research related to the peripheral circulation Such problems as steady flow of liquid through cylindrical tubes, properties of viscosity of blood turbulence pulsatile flow flowmeters elastic properties of arterial walls impedance and wave reflection are among the many aspects of hemodynamic phenomena discussed by McDonald These complex principles are discussed very well and the many gaps in our knowledge become evident to the reviewer of the book Clinicians will find this extremely technical unless they are well informed in the principles of hydraulics. This is an important contribution to an important subject of circulation of blood in arteries

Drug Induced Clinical Toxicity volume I and II Edited by F Gilbert McMahon M D Mount Kisco New York 1974 Futura Publishing Co 186 pages

McMahon has edited a series of volumes on the principles and techniques of human research and therapeutics These first two volumes *are extremely important and valuable* The others to follow will include additional information on the subject of drug evaluation and use These two volumes are of interest to cardiologists in practice and especially to those conducting drug studies related to the heart and circulation The use of drugs involves all a*spects of medical practice* The evaluation and introduction of new drugs concerns all physicians and their patients These volumes represent the proceedings of a clinical pharmacology symposium held in New Orleans during March 1973 The contributors represent *outstanding people from medical schools* industry and the U S Government The subjects included are extensive The first two volumes readily indicate that the entire series will represent an encyclopedic source of information in one of the important fields of therapeutics and medical practice Prac*ticing physicians* pharmacologists pharmaceutical industry Government and many others concerned with drug studies will find these two volumes extremely valuable

Alexis Carrel Visionary Surgeon By W Sterling Edwards, M D and Peter D Edwards Springfield *1974 Bannerstone* House 143 pages

This is an interesting and well written brief biograph*y of an* important man Vascular and cardiac surgeons should be especially interested in reading and owning a copy Carrel performed important pioneering vascular surgery and developed the early and fundamental techniques Those who knew Carrel personally will find this account *to be reliable* Carrel was an interesting man and his personality is evident from this book The style of presentation is clear and simple so that the reader finds the biography so interesting that he does not want to put the book down before he completes it Fortunately *Charles Lindbergh a close good friend of Carrel* was able to write an interesting foreword before his recent death

Author index*

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Announcements

Purdue Defibrillation Conference

The Biomedical Engineering Center of Purdue University will hold a conference in Lafayette Indiana from October 1 to 3 1975 covering the practical and clinical aspects of cardiac defibrillation The speakers have been selected based upon their positions as leaders in their respective fields The topics to be discussed include clinical basic science and engineering aspects of electrical defibrillation as it pertains to the needs of physicians nurses emergency medical personnel hospital engineers equipment manufacturers and research scientists The state of the art of defibrillation techniques will be presented and examined critically and a major goal of this three day conference will be to integrate all available technology for optimization of ventricular defibrillation The registration fee of $95 includes admission to the proceedings and two luncheons

For further information please write Division of Conferences and Continuation Services Stewart Center Purdue University West Lafayette Indiana 47907 Telephone (317) 749 2033

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